Desmopressin is a transfusion sparing option to reverse platelet dysfunction in patients with severe traumatic brain injury

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BACKGROUND: Platelet dysfunction (PD) is an independent predictor of mortality in patients with severe traumatic brain injury (sTBI). Platelet transfusions (PLTs) have been shown to be an effective treatment strategy to reverse platelet inhibition. Their use is contingent on availability and may be associated with increased cost and transfusion-related complications, making desmopressin (DDAVP) attractive. We hypothesized that DDAVP would correct PD similarly to PLTs in patients with sTBI.

METHODS: This retrospective study evaluated all blunt trauma patients admitted to an urban, level 1 trauma center from July 2015 to October 2016 with sTBI (defined as head abbreviated injury scale [AIS] ≥3) and PD (defined as adenosine diphosphate [ADP] inhibition ≥60% on thromboelastography) and subsequently received treatment. Per our institutional practice, patients with sTBI and PD are transfused one unit of apheresis platelets to reverse inhibition. During a platelet shortage, we interchanged DDAVP for the initial treatment. Patients were classified as receiving DDAVP or PLT based on the initial treatment.

RESULTS: A total of 57 patients were included (DDAVP, n = 23; PLT, n = 34). Patients who received DDAVP were more severely injured (injury severity score, 29 vs. 23; $p = 0.045$), but there was no difference in head AIS (4 vs. 4, $p = 0.16$). There was no difference between the two groups in admission platelet count ($244 \pm 68 \times 10^3/\mu L$ vs. $265 \pm 66 \times 10^3/\mu L$, $p = 0.24$) or other coagulation parameters such as prothrombin time, partial thromboplastin time, or international normalized ratio. Before treatment, both groups had similar ADP inhibition as measured by thromboelastography (ADP, 86% vs. 89%, $p = 0.34$). After treatment, both the DDAVP and PLT groups had similar correction of platelet ADP inhibition ($p = 0.28$).

CONCLUSION: In patients with severe traumatic brain injury and PD, DDAVP may be an alternative to PLTs to correct PD. (*J Trauma Acute Care Surg.* 2020;88: 80–86. Copyright © 2019 American Association for the Surgery of Trauma.)

LEVEL OF EVIDENCE: Therapeutic, level IV.

KEY WORDS: Platelet dysfunction; TBI; DDAVP; TEG; platelet transfusion.

Traumatic brain injury (TBI) remains a major cause of mortality in the United States, affecting more than 1 million people each year.[1] In 2013, the Centers for Disease Control and Prevention estimated that approximately 2.8 million of the country's emergency department visits, hospitalizations, and deaths were related to TBIs.[2] Many studies suggest that an acquired coagulopathy develops in TBI patients.[3–8] In a recent systematic review, incidences of coagulopathy were reported as high as 33% in all TBI patients and up to 60% in those with severe TBI (sTBI).[9]

The degree of coagulopathy appears to be related to the severity of brain injury, and identification of coagulopathy on admission in TBI patients is associated with worse outcomes.[6,10–13] Talving et al.[7] found up to a 10-fold increase in mortality in TBI patients who develop coagulopathy during their hospital course. Coagulopathy can be diagnosed with either conventional assays such as international normalized ratio (INR), partial thromboplastin time (PTT), fibrinogen level, and platelet count[6,10–13] or with more dynamic studies such viscoelastic assays, which include thromboelastography (TEG). Thromboelastography analyzes the kinetics and stability in clot formation and with the addition of platelet mapping (thromboelastography–platelet mapping [TEG-PM]) assesses clot strength and platelet response to different agonists.[14]

The mechanism behind the coagulation disorders associated with TBI is complex and not fully understood.[3,7,9,15,16] Some authors believe that it is related to increased tissue factor release, disseminated intravascular coagulation, platelet dysfunction (PD), and activation of protein C pathways.[12,15,17,18] One study proposed that injury to brain tissues leads to increased release of tissue factor into systemic circulation and overactivation of the coagulation cascade causing excess thrombin formation thus increasing platelet activation.[19] This significant increase in platelet activation does not appear to influence platelet count but instead produces platelets with decreased hemostatic abilities, contributing to the coagulopathy seen in TBI patients.[16]

Previously, our institution showed that PD, defined as adenosine diphosphate (ADP) inhibition of 60% or greater on TEG-PM, is an independent predictor of increased mortality in patients with sTBI.[20] These findings led to a practice change at our institution, which included platelet transfusions (PLTs) for patients admitted to the surgical intensive care unit (ICU) with TBI who exhibited ADP inhibition of 60% or greater. We subsequently were able to show PLTs to be an effective treatment strategy to reverse platelet inhibition and that treating this PD may reduce mortality in patients with sTBI.[21] During a period of platelet shortage, our

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institution substituted desmopressin (1-deamino-8-D-arginine vasopressin; DDAVP) for platelets as our initial therapy of choice for PD in patients with sTBI. We hypothesized that DDAVP would correct PD similarly to PLTs in patients with sTBI.

PATIENTS AND METHODS

This was a retrospective study of all adult blunt trauma patients who sustained an intracranial hemorrhage and were admitted to our American College of Surgeons (ACS)-verified level 1 trauma center from July 2015 to October 2016. Per our institutional practice, patients with sTBI and PD are transfused one unit of apheresis platelets to reverse inhibition. If platelet inhibition persists on repeat TEG, after this first round of transfusion, the patient then receives a second round of PLT. A completion TEG is obtained to evaluate effect of transfusion, but no further transfusions are performed for continued PD identified on TEG. During a platelet shortage, we interchanged DDAVP for the initial treatment in this algorithm (Fig. 1). Patients were included if they sustained an sTBI (defined as head AIS ≥3), displayed PD (defined as ≥60% inhibition on the ADP platelet pathway) as measured by TEG-PM drawn at admission to the ICU, received either DDAVP or PLT as the initial therapy for PD, and had a repeat TEG after intervention for PD. Patients were excluded if the time to first TEG or between TEGs exceeded 24 hours, if hemostatic agents were given before first TEG, or if DDAVP was coadministered with the PLTs. Study patients with sTBI and platelet inhibition who received a PLT or DDAVP infusion were compared.

Data collection included patient demographics, admission physiology, injury severity score (ISS), head AIS, prothrombin time (PT), INR, PTT, platelet count, admission sodium (Na) level, lowest Na level within 24 hours of admission, and preinjury antiplatelet therapy. Thromboelastography-specific variables included split point (SP), Reaction (R) time (*R*), Kinetics (K) time (*K*), α angle (angle), maximum amplitude (MA), *G* value (*G*), estimated percent lysis, and platelet assay variables including ADP and arachidonic acid (AA) inhibition. The primary outcome was correction of ADP inhibition. Secondary outcomes included mortality as well as hospital and ICU length of stay.

Baseline characteristics and outcomes data were analyzed using χ^2 with Yates correction for categorical variables and unpaired Student *t* test or Wilcoxon rank sum test for continuous parametric and nonparametric data, respectively. A generalized linear model (GLM) procedure was used to compare serial TEG parameters following PLTs. Values are reported as mean ± SD or raw percentages. An a priori α value of 0.05 was identified for statistical significance. This study was approved by our local institutional review board.

RESULTS

A total of 57 patients with sTBI and PD who received either DDAVP infusion or PLT during our study period were included (DDAVP, n = 23; PLT, n = 34). When comparing the DDAVP to the PLT group (Table 1), those in the PLT group were more often Caucasian (65% vs. 94%, $p = 0.005$), but there was no significant difference in age (41 vs. 40, $p = 0.86$) or male sex (74% vs. 82%, $p = 0.44$). Because our groups significantly differed in their racial composition, we used a logistic regression to evaluate the effect of being Caucasian between groups on their ability to correct their ADP dysfunction to less than 60%. This showed that being Caucasian was not significantly associated with correction of ADP inhibition (odds ratio, 1.1; 95% confidence interval, 0.21–5.77; $p = 0.91$).

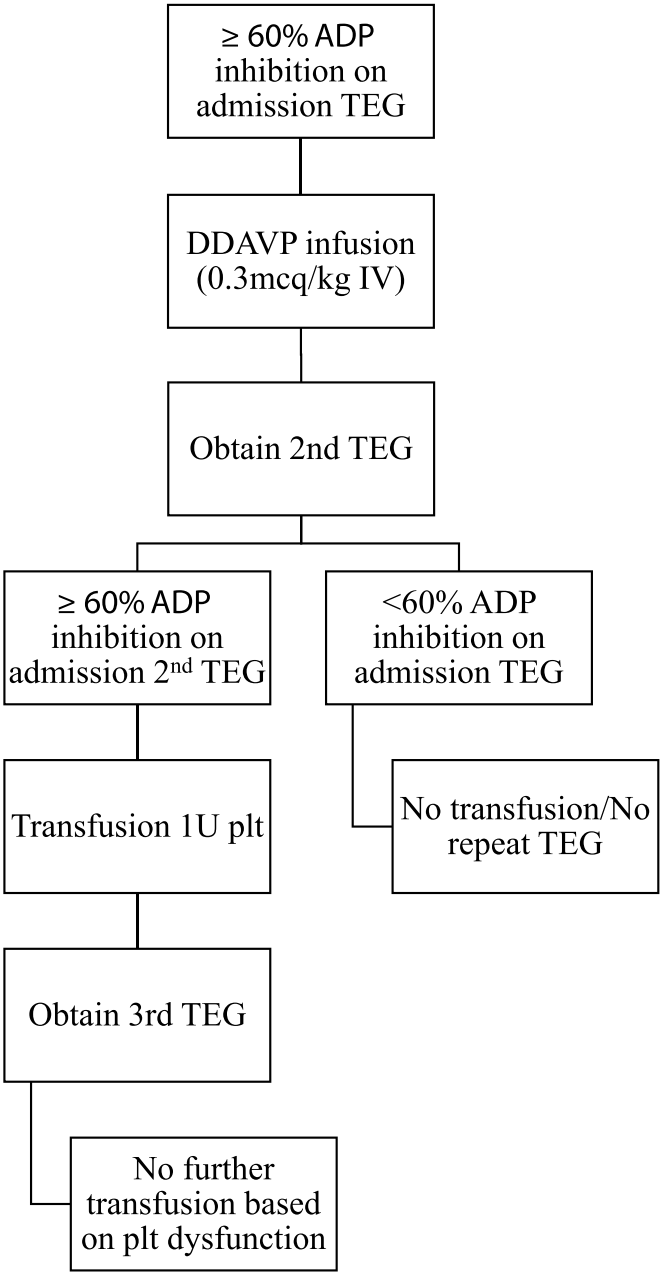

Figure 1. Algorithm for treatment of PD in TBI patients diagnosed on TEG. In patients with TBI with admission TEG showing ADP inhibition of 60% or greater, they would be transfused DDAVP (0.3 μq/kg intravenous). The TEG would be repeated, and if ADP inhibition had corrected to less than 60%, no further transfusions based on TEG would occur. If on the second TEG, there was continued ADP inhibition of 60% or greater, then patients would be transfused with 1U platelets. The third TEG was obtained to evaluate response, but no further treatment would occur based on the third TEG.

TABLE 1. Demographic Comparison by Cohort

	DDAVP Group, n = 23	PLT Group, n = 34	*p*
Age, mean ± SD, y	41 ± 22	40 ± 17	0.86
Male	17 (74)	28 (82)	0.44
White	15 (65)	32 (94)	0.005
Prehospital systolic, mm Hg	137 ± 34	152 ± 29	0.17
Prehospital pulse, bpm	103 ± 21	103 ± 30	0.99
Prehospital GCS	9 ± 5	9 ± 5	0.58
ED respiratory rate	19 ± 8	16 ± 10	0.42
Hypotension (SBP ≤90 mm Hg)	1 (5)	4 (12)	0.64
ED SBP, mm Hg	138 ± 28	142 ± 36	0.68
ED pulse, bpm	97 ± 24	105 ± 31	0.30
ED GCS	9 ± 5	9 ± 6	0.77
AIS head	4 ± 0.90	4 ± 0.77	0.16
AIS face	0.70 ± 0.93	0.76 ± 1.1	0.80
AIS chest	0.87 ± 1.4	0.94 ± 1.3	0.84
AIS abdomen	0.43 ± 0.99	0.15 ± 0.50	0.15
AIS extremities	0.91 ± 1.3	0.79 ± 1.1	0.72
AIS external	0.65 ± 0.65	0.85 ± 0.61	0.24
ISS	29 ± 12	23 ± 9	0.045
Dead	5 (22)	3 (9)	0.25
Hospital LOS, d	15 ± 10	15 ± 18	0.90
ICU LOS, d	8 ± 5	9 ± 14	0.79
Ventilation days	5 ± 5	3 ± 5	0.19
Admission platelet count, $\times 10^3/\mu L$	244 ± 68	265 ± 66	0.24
Admission PT, s	12.4 ± 2.2	11.8 ± 1.9	0.31
Admission INR	1.07 ± 0.19	1.03 ± 0.17	0.41
Admission PTT, s	27.5 ± 7.6	28.8 ± 5.5	0.46
Preinjury antiplatelet therapy	2 (9)	3 (9)	0.65
ΔNa, mmol/L	−1.9 ± 3.9	−0.94 ± 4.1	0.38

Description of each cohort regarding demographics, operative interventions, coagulation parameters, prehospital antiplatelet therapy, and blood products given.
ED, emergency department; LOS, length of stay.

When comparing the DDAVP group with PLT group, there was no difference in admission heart rate (97 ± 24 vs. 105 ± 31, $p = 0.30$), hypotension (5% vs. 12%, $p = 0.64$), or Glasgow Coma Scale (GCS) (9 ± 5 vs. 9 ± 6, $p = 0.77$). Patients who received DDAVP were more severely injured (ISS, 29 ± 12 vs. 23 ± 9, $p = 0.045$), but there was no difference in head AIS (4 ± 0.90 vs. 4 ± 0.77, $p = 0.16$).

When comparing traditional coagulation parameters, there was no difference in admission platelet count (244 ± 68 × $10^3/\mu L$ vs. 265 ± 66 × $10^3/\mu L$, $p = 0.24$), PT (12.4 ± 2.2 seconds vs. 11.8 ± 1.9 seconds, $p = 0.31$), INR (1.07 ± 0.19 vs. 1.03 ± 0.17, $p = 0.41$), PTT (27.5 ± 7.6 seconds vs. 28.8 ± 5.5 seconds, $p = 0.46$), or rate of preinjury antiplatelet therapy (9% vs. 9%, $p = 0.65$). We compared sodium levels before and within 24 hours of therapy and evaluated the change in sodium associated with each intervention. There was no significant difference between groups (−1.9 mmol/L vs. −0.94 mmol/L, $p = 0.38$).

Following treatment, clot strength improved to a greater degree following PLT compared with DDAVP, as represented by decreased SP, increased α angle, MA, and *G* value (Table 2). Desmopressin administration appeared to correct ADP inhibition to a similar degree as PLT (−24.9 ± 25 vs. −18.5 ± 19, $p = 0.28$) (Fig. 2). Following one round of DDAVP infusion, 57% of patients had correction of their ADP inhibition to less than 60% as compared with 32% of patients who underwent PLT. There was no significant difference between in-hospital all-cause mortality between the two groups (22% vs. 9%, $p = 0.25$).

DISCUSSION

To date, no strong evidence exists regarding the treatment of platelet-driven coagulopathy in TBI patients. It is still unclear whether the presence of PD in this patient population is a prognostic indicator or a therapeutic target. Generally, treatment options for any coagulopathy should target the underlying cause. There still continues to be a knowledge gap regarding the etiology of the PD that develops in TBI patients, which makes treatment in these patients more difficult. Desmopressin has long been used as an adjunct for treatment in coagulopathy and has been validated in its use for congenitally acquired coagulopathies such as von Willebrand disease and hemophilia type A. In our current study, we were able to show that DDAVP corrects PD to a similar extent as PLTs in patients with sTBI. To understand the mechanism of action of DDAVP in bleeding disorders, it is important to recognize specific steps of the coagulation cascade. After endothelial disruption, platelets adhere to subendothelial collagen through platelet surface glycoprotein receptors (GPIb-V-IX) and von Willebrand factor (vWF). These adherent platelets undergo a process of degranulation releasing ADP, histamine, serotonin, Thromboxane A2 (TXA2), platelet derived growth factor (PDGF), platelet factors (including platelet factor VIII; FVIII), and other components. Adenosine diphosphate and TXA2 act as stimuli for platelet aggregation and platelet plug formation.[22,23] Desmopressin works as a hemostatic agent by increasing the release of FVIII and vWF levels in the body, which are major contributors to intrinsic coagulation cascade and primary hemostasis.[24] Many studies have shown that the use of DDAVP increases these factors about two- to sixfold.[25,26]

The evidence surrounding the use and efficacy of DDAVP in treating congenital bleeding disorders is strong,[27,28] and many studies have further validated its use in acquired bleeding disorders. In 1983, Mannucci et al.[29] conducted a double-blind controlled study examining the effects of DDAVP versus placebo on bleeding time in uremic patients. He showed that after DDAVP infusion all patients had improved bleeding times.[29] He went on to perform another randomized control trial evaluating both acquired and congenital disorders associated with prolonged bleeding times and their response to DDAVP. This study showed that DDAVP was able to significantly shorten the bleeding times in patients with cirrhosis, those taking antiplatelet drugs, and those with an unclassified disorder causing prolonged bleeding times.[30] When focusing on DDAVP effect on patients taking antiplatelet agents, Cattaneo et al.[31] was able to show that, after giving healthy patients ticlopidine, an ADP receptor inhibitor, DDAVP was able to significantly improve these patients' bleeding times. Levine et al.[32] was able to show similar results using an animal model where rats were given clopidogrel, and this study showed that DDAVP was able to partially reverse clopidogrel-induced PD. Koscielny et al.[33] identified 254 patients with either acquired or inherited coagulopathy undergoing elective surgery and prospectively studied

TABLE 2. TEG Variable

	DDAVP Group			PLT Group			
TEG Variable	**TEG1**	**TEG2**	**Δ**	**TEG1**	**TEG2**	**Δ**	***p****
SP, min	3.4 ± 0.84	4.1 ± 1.5	0.71 ± 1.3	3.9 ± 1.3	3.8 ± 0.82	−0.09 ± 1.5	0.045
Reaction time (*r*), min	3.7 ± 0.92	4.4 ± 1.7	0.69 ± 1.5	4.3 ± 1.4	4.1 ± 0.88	−0.17 ± 1.7	0.06
Clot formation time (*K*), min	3.3 ± 8.4	1.8 ± 0.72	−1.5 ± 8.4	1.6 ± 0.76	1.1 ± 0.22	−0.50 ± 0.71	0.49
Angle (α), degree	69.2 ± 5.4	67.1 ± 7.7	−2.1 ± 6	68.5 ± 7	73.8 ± 2.9	5.4 ± 6.3	<0.0001
MA, mm	62.5 ± 5.5	61.3 ± 5.9	−1.2 ± 3.8	63 ± 6.8	67.8 ± 4.2	4.8 ± 6.1	<0.0001
G value, dynes/cm^2	8.6 ± 2.0	8.3 ± 2	−0.34 ± 1.4	8.9 ± 2.4	10.8 ± 2.1	1.8 ± 2.1	<0.0001
EPL, %	0.90 ± 1.5	0.70 ± 1.1	−0.19 ± 1.4	2.5 ± 3.9	2.4 ± 2.7	−0.11 ± 3.7	0.92
ADP inhibition, %	85.7 ± 12.0	60.8 ± 26.4	−24.9 ± 25	88.9 ± 12.7	70.3 ± 21.7	−18.5 ± 19	0.28
AA inhibition, %	45.2 ± 32.5	33.4 ± 28.2	−11.8 ± 34.0	40.3 ± 33.1	30.9 ± 28.7	−9.9 ± 22.0	0.80

*p Value is comparing change in TEG parameters between PT and DDAVP group.
Before (TEG1) and after (TEG2) intervention (mean ± SD).
Baseline TEG (TEG1) was obtained on admission to the ICU. Second TEG (TEG2) was obtained following one round of PLT or DDAVP infusion. The changes between TEG1 and TEG2 for each parameter were then compared, and these values (Δ) for DDAVP and PLT groups were compared.
EPL, estimated percent lysis; MA, maximum amplitude.

the preoperative use of DDAVP to correct this coagulopathy. This study found that preoperative DDAVP therapy led to correction of PD in 90.2% of patients with 66.9% showing correction of the ADP pathway.[33] This collective body of literature supports the efficacy surrounding the use of DDAVP in both congenital and acquired bleeding disorders.

When specifically looking at patients with intracranial hemorrhage, Kapapa et al.[34] concluded that DDAVP was able to stabilize platelet function in neurosurgical patients with intracranial hemorrhage who had received aspirin. Naidech et al.[35] also found that patients with acute intracerebral hemorrhage with abnormal platelet activity or known aspirin use had improved platelet activity after DDAVP infusion. There is very little information regarding the use of DDAVP in PD in trauma patients and none, to our knowledge, regarding its use in the PD associated with sTBI. Our current study not only confirms the ability of DDAVP to reverse acquired PD to a similar degree as platelets but also shows that DDAVP is effective in reversing PD associated with sTBI. It is still uncertain whether this reversal is associated with improved clinical outcomes, and further research in this field is needed to answer that question.

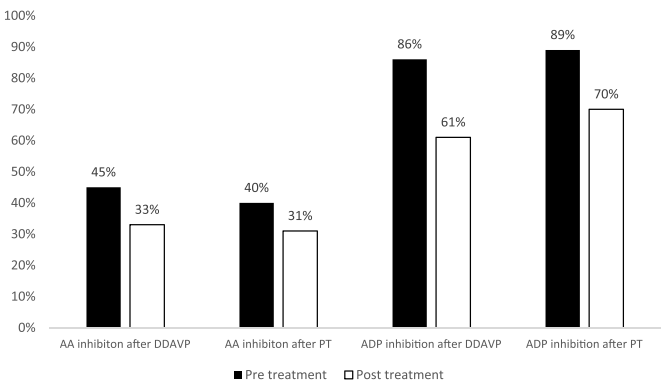

Figure 2. Visual representation of the change in platelet ADP inhibition along the AA ($p = 0.80$) and ADP ($p = 0.28$) pathways after DDAVP and PLT.

A lot of debate still exists surrounding the utility of different TEG parameters, such as ADP inhibition, as prognostic indicators or therapeutic targets in trauma patients. Stettler et al.[36] assessed ADP inhibition in severely injured trauma patients. In this study, they analyzed the predictive value of admission ADP inhibition level and found that in all severely injured trauma patients ADP inhibition was not predictive of mortality or need for massive transfusion or for PLT.[36] The big difference between this study and our current study is the population. We examined only sTBI patients, while this study analyzed all severely injured trauma patients. As discussed earlier, PD is implicated in the mechanism leading to the acquired coagulopathy seen in TBI patients. We believe that trauma patients in general behave differently than TBI patients, so while this study was unable to show a predictive value in ADP inhibition, there have been data to support the use of ADP inhibition in sTBI patients as a prognosticator.[20] Holzmacher et al.[37] looked at all TBI patients on preinjury antiplatelet therapy and evaluated both those who were transfused with platelets and those who were not to see the effect PLTs had on TEG parameters and CT progression. They found that PLTs improved both AA and ADP inhibition, but only AA inhibition improved significantly. They saw no improvement in mortality using PLTs in this population.[37] Again, this supports further need for larger randomized controlled trials to thoroughly evaluate the therapeutic value of PLTs in patients with TBI.

One notable finding from our current study was the difference in improvement of TEG-PM parameters in those receiving DDAVP versus platelets. The PLT group corrected almost every element of the TEG-PM including our primary outcome of correction of ADP, while DDAVP only showed significant correction of ADP inhibition. When giving a closer look into the components of apheresis platelets, this result is not unexpected. Each unit of platelets contains about 50 mL of plasma likely resulting in a more broad improvement in TEG-specific variables as compared with DDAVP.[38] We are unsure if this more robust effect on the overall TEG confers any benefit to patients.

With ongoing shortages of blood products and the significant adverse reactions associated with allogeneic transfusions, methods to limit blood product use are important. More than

1 million units of platelets are transfused in the United States each year and more than 2 million in Europe.[39,40] Platelet transfusions can lead to a spectrum of transfusion reactions,[41] the most common and most mild of these include fever, chills, hives, and itching. These reactions normally are self-limiting and resolve with little or no treatment. Severe reactions, some of which have the potential to be life threatening, associated with PLT include infection, transfusion-related acute lung injury, transfusion-associated circulatory overload, and anaphylactic reactions.[42,43] Although rare, a 2016 study involving PLTs in France found that approximately 6 per 1000 transfusions with apheresis platelets were associated with adverse reactions.[44] In addition to risk, utilization of allogeneic blood products, such as platelets, have the potential to delay therapy. These products require compatibility testing and, at most institutions, are not readily accessible. Even in the cases of traumatic bleeding, when blood product availability should be prioritized, the average time to administration of platelets has been reported to be 2 to 3 hours.[45] All of these factors have led to the investigation of alternative agents to use as adjunctive or substitutive therapy to blood products.

In general, DDAVP appears to be a well-tolerated and relatively safe pharmaceutical agent.[46] Desmopressin is a synthetic analog of vasopressin, and because it is not an allogeneic blood component, there are fewer significant risks associated with its use. There are a number of mild adverse effects described with the use of DDAVP, and most are very nonspecific symptoms.[42] The most well described and severe adverse effect of this medication is hyponatremia, which corresponds with its well-known antidiuretic property. This electrolyte abnormality becomes important in TBI patients because it relates to intracranial pressure (ICP). Many of therapies directed at lowering ICP ultimately do this by causing hypernatremia, ultimately drawing fluid off the brain leading to decreased edema and thus pressure. In these patients, significant reduction in sodium level would be worrisome because this could lead to increased ICP and ultimately worse outcomes. Most existing literature on DDAVP-induced hyponatremia related to its use in the treatment of nocturnal enuresis.[47,48] In a systematic review looking at hyponatremia associated with DDAVP in these patients, only 54 cases of severe hyponatremia were identified.[49] Other studies evaluating the efficacy and safety of DDAVP have found only mild decreases in serum sodium levels, especially in those receiving only a single dose.[50,51] The half-life of DDAVP is 2 to 4 hours, making the duration of action about 6 to 14 hours,[42] so effects of a single dose are expected to be seen within the first 24 hours of administration. In our current cohort, we were unable to show a statistically significant difference in sodium change before and after therapy with either DDAVP or PLTs. Overall, as compared with PLTs, DDAVP appears to be associated with less adverse effects and is tolerated more favorably by patients.

Another important factor to consider when comparing two therapeutic options is cost. Desmopressin appears to be a more cost-effective option than platelets. The Lexicomp published price of injectable DDAVP is US $12.34 to US $70.55 for 4 μg/1 mL. During our study, we used a dose of 0.3 μg/kg, so using this pricing, the cost of DDAVP in a patient of average weight, ranged from US $65 to US $370.[42] This is significantly cheaper than a unit of apheresis platelets which costs, on average, about US $534.[52]

Several limitations of this study can be attributed to the inherent retrospective design. We relied on the accuracy and heterogeneous documentation practices in the medical chart and/or the trauma registry. We would have liked to have more information related to vWF levels and activity, ICP data, and osmolarity but our data collection was limited to what was captured by our trauma registry. The TEG-PM utilization was not an automated process, and ordering of this test was subject to the physician discretion, which may have influenced patient selection, thus creating a bias. Another limitation was our heterogeneous groups, which may have influenced our results. Specific to this, our DDAVP group was more severely injured than our PLT group. The increased severity of nonbrain injuries may have resulted in influences on TEG-PM and some of our secondary outcomes such as mortality. The racial difference in groups may also have been a confounding factor because some sources have implicated race in differences in platelet biology.[53] We did attempt to address this by performing a logistic regression to better understand the racial influence in the ability of patients to correct their ADP dysfunction. Although our regression showed that the ability to correct ADP dysfunction was independent of race, a better study design is necessary to more effectively evaluate this. Another significant limitation was our small sample size, which may have skewed our overall results and conclusions.

CONCLUSIONS

In patients with sTBI and PD, DDAVP may be an alternative to PLTs to correct PD. Given the improved safety profile, reduced cost, and comparable correction of PD, DDAVP appears to be an attractive alternative for therapy in patients with sTBI and PD. More research, including randomized controlled trials, is needed to more strongly validate the effectiveness of DDAVP to correct PD in patients with sTBI and establish its ability to influence clinical outcomes such as mortality.

AUTHORSHIP

E.F., M.J.D., and C.V.R.B. contributed in the literature review. E.F., M.J.D., P.G.T., T.B.C., J.D.A., and C.V.R.B. contributed in the study design. E.F., P.S., M.J.D., P.G.T., T.B.C., J.D.A., and C.V.R.B. contributed in the data collection. E.F., M.J.D., P.G.T., T.B.C., J.D.A., S.A., and C.V.R.B. contributed in the data analysis. E.F., M.J.D., P.G.T., T.B.C., J.D.A., and C.V.R.B. contributed in the data interpretation. E.F., M.J.D., and C.V.R.B. contributed in the article writing. E.F. and C.V.R.B. contributed in the critical revision.

DISCLOSURE

The authors declare no conflicts of interest.

REFERENCES

1. Rutland-Brown W, Langlois JA, Thomas KE, Xi YL. Incidence of traumatic brain injury in the United States, 2003. *J Head Trauma Rehabil*. 2006;21(6):544–548.
2. Taylor CA, Bell JM, Breiding MJ, Xu L. Traumatic brain injury-related emergency department visits, hospitalizations, and deaths — United States, 2007 and 2013. *MMWR Surveill Summ*. 2017;66(9):1–16.
3. Maegele M, Schöchl H, Menovsky T, Maréchal H, Marklund N, Buki A, Stanworth S. Coagulopathy and haemorrhagic progression in traumatic brain injury: advances in mechanisms, diagnosis, and management. *Lancet Neurol*. 2017;16(8):630–647.

4. de Oliveira Manoel AL, Neto AC, Veigas PV, Rizoli S. Traumatic brain injury associated coagulopathy. *Neurocrit Care*. 2015;22(1):34–44.
5. Epstein DS, Mitra B, Cameron PA, Fitzgerald M, Rosenfeld JV. Acute traumatic coagulopathy in the setting of isolated traumatic brain injury: definition, incidence and outcomes. *Br J Neurosurg*. 2014;1–5.
6. Wafaisade A, Lefering R, Tjardes T, Wutzler S, Simanski C, Paffrath T, Fischer P, Bouillon B, Maegele M, Trauma Registry of DGU. Acute coagulopathy in isolated blunt traumatic brain injury. *Neurocrit Care*. 2010;12(2): 211–219.
7. Talving P, Benfield R, Hadjizacharia P, Inaba K, Chan LS, Demetriades D. Coagulopathy in severe traumatic brain injury: a prospective study. *J Trauma*. 2009;66(1):55–61; discussion 61–2.
8. Yuan Q, Sun YR, Wu X, Yu J, Li ZQ, Du ZY, Wu XH, Zhou LF, Hu J. Coagulopathy in traumatic brain injury and its correlation with progressive hemorrhagic injury: a systematic review and meta-analysis. *J Neurotrauma*. 2016;33(14):1279–1291.
9. Harhangi BS, Kompanje EJ, Leebeek FW, Maas AI. Coagulation disorders after traumatic brain injury. *Acta Neurochir*. 2008;150(2):165–175; discussion 175.
10. Oertel M, Kelly DF, McArthur D, Boscardin WJ, Glenn TC, Lee JH, Gravori T, Obukhov D, McBride DQ, Martin NA. Progressive hemorrhage after head trauma: predictors and consequences of the evolving injury. *J Neurosurg*. 2002;96(1):109–116.
11. Stein SC, Young GS, Talucci RC, Greenbaum BH, Ross SE. Delayed brain injury after head trauma: significance of coagulopathy. *Neurosurgery*. 1992;30(2):160–165.
12. Stein SC, Smith DH. Coagulopathy in traumatic brain injury. *Neurocrit Care*. 2004;1(4):479–488.
13. Halpern CH, Reilly PM, Turtz AR, Stein SC. Traumatic coagulopathy: the effect of brain injury. *J Neurotrauma*. 2008;25(8):997–1001.
14. Collyer TC, Gray DJ, Sandhu R, Berridge J, Lyons G. Assessment of platelet inhibition secondary to clopidogrel and aspirin therapy in preoperative acute surgical patients measured by Thrombelastography® Platelet Mapping™. *Br J Anaesth*. 2009;102(4):492–498.
15. Laroche M, Kutcher ME, Huang MC, Cohen MJ, Manley GT. Coagulopathy after traumatic brain injury. *Neurosurgery*. 2012;70(6):1334–1345.
16. Castellino FJ, Chapman MP, Donahue DL, et al. Traumatic brain injury causes platelet adenosine diphosphate and arachidonic acid receptor inhibition independent of hemorrhagic shock in humans and rats. *J Trauma Acute Care Surg*. 2014;76(5):1169–1176.
17. Stein SC, Chen XH, Sinson GP, Smith DH. Intravascular coagulation: a major secondary insult in nonfatal traumatic brain injury. *J Neurosurg*. 2002;97(6):1373–1377.
18. Nekludov M, Bellander BM, Blombäck M, Wallen HN. Platelet dysfunction in patients with severe traumatic brain injury. *J Neurotrauma*. 2007;24(11): 1699–1706.
19. Jacoby RC, Owings JT, Holmes J, Battistella FD, Gosselin RC, Paglieroni TG. Platelet activation and function after trauma. *J Trauma*. 2001;51(4):639–647.
20. Daley MJ, Enright Z, Nguyen J, Ali S, Clark A, Aydelotte JD, Teixeira PG, Coopwood TB, Brown CV. Adenosine diphosphate platelet dysfunction on thromboelastogram is independently associated with increased morality in traumatic brain injury. *Eur J Trauma Emerg Surg*. 2017;43(1):105–111.
21. Furay E, Daley M, Teixeira PG, Coopwood TB, Aydelotte JD, Malesa N, Tellinghuisen C, Ali S, Brown LH, Brown CVR. Goal-directed platelet transfusions correct platelet dysfunction and may improve survival in patients with severe traumatic brain injury. *J Trauma Acute Care Surg*. 2018;85(5): 881–887.
22. Beshay JE, Morgan H, Madden C, Yu W, Sarode R. Emergency reversal of anticoagulation and antiplatelet therapies in neurosurgical patients. *J Neurosurg*. 2010;112(2):307–318.
23. Palta S, Saroa R, Palta A. Overview of the coagulation system. *Indian J Anaesth*. 2014;58(5):515–523.
24. WFH. Desmopressin (DDAVP) in the Treatment of Bleeding Disorders. Available at: http://www1.wfh.org/publication/files/pdf-1131.pdf. Accessed August 15, 2018.
25. Svensson PJ, Bergqvist PB, Juul KV, Berntorp E. Desmopressin in treatment of haematological disorders and in prevention of surgical bleeding. *Blood Rev*. 2014;28(3):95–102.
26. Franchini M. The use of desmopressin as a hemostatic agent: a concise review. *Am J Hematol*. 2007;82(8):731–735.
27. Carless PA, Henry DA, Moxey AJ, O'Connell D, McClelland B, Henderson KM, Sly K, Laupacis A, Fergusson D. Desmopressin for minimising perioperative allogeneic blood transfusion. *Cochrane Database Syst Rev*. 2004;(1):CD001884.
28. Crescenzi G, Landoni G, Biondi-Zoccai G, et al. Desmopressin reduces transfusion needs after surgery: a meta-analysis of randomized clinical trials. *Anesthesiology*. 2008;109(6):1063–1076.
29. Mannucci PM, Remuzzi G, Pusineri F, Lombardi R, Valsecchi C, Mecca G, Zimmerman TS. Deamino-8-D-arginine vasopressin shortens the bleeding time in uremia. *N Engl J Med*. 1983;308(1):8–12.
30. Mannucci PM, Vicente V, Vianello L, Cattaneo M, Alberca I, Coccato MP, Faioni E, Mari D. Controlled trial of desmopressin in liver cirrhosis and other conditions associated with a prolonged bleeding time. *Blood*. 1986;67(4): 1148–1153.
31. Cattaneo M, Lombardi R, Bettega D, Lecchi A, Mannucci PM. Shear-induced platelet aggregation is potentiated by desmopressin and inhibited by ticlopidine. *Arterioscler Thromb*. 1993;13(3):393–397.
32. Levine M, Swenson S, McCormick T, Henderson SO, Thomas SH, Markland FS. Reversal of thienopyridine-induced platelet dysfunction following desmopressin administration. *J Med Toxicol*. 2013;9(2):139–143.
33. Koscielny J, von Tempelhoff G-F, Ziemer S, Radtke H, Schmutzler M, Sinha P, Salama A, Kiesewetter H, Latza R. A practical concept for preoperative management of patients with impaired primary hemostasis. *Clin Appl Thromb Hemost*. 2004;10(2):155–166.
34. Kapapa T, Röhrer S, Struve S, Petscher M, König R, Wirtz CR, Woischneck D. Desmopressin acetate in intracranial haemorrhage. *Neurol Res Int*. 2014; 2014:298767.
35. Naidech AM, Maas MB, Levasseur-Franklin KE, et al. Desmopressin improves platelet activity in acute intracerebral hemorrhage. *Stroke*. 2014;45(8):2451–2453.
36. Stettler GR, Moore EE, Moore HB, Nunns GR, Huebner BR, Einersen P, Ghasabyan A, Silliman CC, Banerjee A, Sauaia A. Platelet adenosine diphosphate receptor inhibition provides no advantage in predicting need for platelet transfusion or massive transfusion. *Surgery*. 2017;162(6): 1286–1294.
37. Holzmacher JL, Reynolds C, Patel M, et al. Platelet transfusion does not improve outcomes in patients with brain injury on antiplatelet therapy. *Brain Inj*. 2018;32(3):325–330.
38. Thiagarajan P, Afshar-Kharghan V. Platelet transfusion therapy. *Hematol Oncol Clin North Am*. 2013;27(3):629–643.
39. Whitaker BI, Rajbhandary S, Harris A. The 2013 AABB Blood Collection, Utilization, and Patient Blood Management Survey Report. American Association of Blood Banks. 2015. Available at: http://www.aabb.org/research/hemovigilance/ bloodsurvey/Pages/default.aspx. Accessed August 10, 2018.
40. Van Hoeven LR, Janssen MP, Rautmann G. The Collection, Testing and Use of Blood and Blood Components in Europe, 2012 Report. European Directorate for the Quality of Medicines and HealthCare of the Council of Europe (EDQM). 2015. Available at: https://www.edqm.eu/sites/default/files/the_collection_testing_and_use_of_blood_and_blood_components_in_europe_2012_report.pdf. Accessed January 20, 2018.
41. Suddock JT, Crookston KP. Transfusion, Reactions. In: *StatPearls*. Treasure Island, FL: StatPearls Publishing; 2018.
42. Desmopressin. Lexicomp Online. 2013. Available at: http://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/6707. Accessed August 10, 2018.
43. Shan Yuan Md. Clinical and Laboratory Aspects of Platelet Transfusion Therapy. UpToDate. 2018. Available at: https://www.uptodate.com/contents/clinical-and-laboratory-aspects-of-platelet-transfusion-therapy?search=platelet%20transfusion&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1#H382870592. Accessed August 10, 2018.
44. Daurat A, Roger C, Gris J, Daurat G, Feissel M, Le Manach Y, Lefrant J, Muller L. Apheresis platelets are more frequently associated with adverse reactions than pooled platelets both in recipients and in donors: a study from French hemovigilance data. *Transfusion*. 2016;56(6):1295–1303.
45. Stanworth SJ, Davenport R, Curry N, et al. Mortality from trauma haemorrhage and opportunities for improvement in transfusion practice. *Br J Surg*. 2016;103(4):357–365.

46. Miesbach W, Krekeler S, Dück O, Llugaliu B, Asmelash G, Schüttrumpf J, Alesci SR, Grossmann R. Clinical assessment of efficacy and safety of DDAVP. *Hamostaseologie*. 2010;30(Suppl 1):S172–S175.
47. Schwab M, Wenzel D, Ruder H. Hyponatraemia and cerebral convulsion due to short term DDAVP therapy for control of enuresis nocturna. *Eur J Pediatr*. 1996;155(S1):46–48.
48. Alloussi SH, Mürtz G, Lang C, Madersbacher H, Strugala G, Seibold J, Schwentner C, Stenzl A, Alloussi S. Desmopressin treatment regimens in monosymptomatic and nonmonosymptomatic enuresis: a review from a clinical perspective. *J Pediatr Urol*. 2011;7(1):10–20.
49. Lucchini B, Simonetti GD, Ceschi A, Lava SA, Faré PB, Bianchetti MG. Severe signs of hyponatremia secondary to desmopressin treatment for enuresis: a systematic review. *J Pediatr Urol*. 2013;9(6 Pt B):1049–1053.
50. Stoof SC, Cnossen MH, de Maat MP, Leebeek FW, Kruip MJ. Side effects of desmopressin in patients with bleeding disorders. *Haemophilia*. 2016;22(1):39–45.
51. Lethagen S, Frick K, Sterner G. Antidiuretic effect of desmopressin given in hemostatic dosages to healthy volunteers. *Am J Hematol*. 1998;57(2):153–159.
52. Toner RW, Pizzi L, Leas B, Ballas SK, Quigley A, Goldfarb NI. Costs to hospitals of acquiring and processing blood in the US: a survey of hospital-based blood banks and transfusion services. *Appl Health Econ Health Policy*. 2011;9(1):29–37.
53. Edelstein LC, Simon LM, Montoya RT, Holinstat M, Chen ES, Bergeron A, Kong X, Nagalla S, Mohandas N, Cohen DE, Dong J-F, Shaw C, Bray PF. Racial differences in human platelet PAR4 reactivity reflect expression of PCTP and miR-376c. *Nat Med*. 2013;19(12):1609–1616.