

**SYSTEMIC ANTICOAGULATION IN THE SETTING OF VASCULAR EXTREMITY TRAUMA****SYSTEMIC ANTICOAGULATION IN THE SETTING OF VASCULAR EXTREMITY TRAUMA**

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## ABSTRACT

**Introduction:** There is conflicting data regarding if patients with vascular extremity trauma who undergo surgical treatment need to be systematically anticoagulated. We hypothesized that intraoperative systemic anticoagulation (ISA) decreased the risk of repair thrombosis or limb amputation after traumatic vascular injury of the extremities.

**Methods:** We analyzed a composite risk of repair thrombosis and/or limb amputation (RTLTA) between patients who did and did not undergo ISA during arterial injury repair. Patient data was collected in the American Association for the Surgery of Trauma PROspective Vascular Injury Treatment (PROOVIT) registry. This registry contains demographic, diagnostic, treatment, and outcome data.

**Results:** Between February 2013 and August 2015, 193 patients with upper or lower extremity arterial injuries who underwent open operative repair were entered into the PROOVIT registry. The majority were male (87%) with a mean age of 32.6 years (range 4-91) and 74% injured by penetrating mechanism. 63% of the injuries were described as arterial transection and 37% had concomitant venous injury. 62% of patients underwent ISA. RTLTA occurred in 22 patients (11%) overall, with no significant difference in these outcomes between patients who received ISA and those that did not (10% vs. 14%,  $p = 0.6$ ). There was, however, significantly higher total blood product use noted among patients treated with ISA versus those that did not receive ISA (median 3 units vs. 1 unit,  $p = 0.002$ ). Patients treated with ISA also stayed longer in the ICU (median 3 days vs. 1 day,  $p = 0.001$ ) and hospital (median 9.5 days vs. 6 days,  $p = 0.01$ ).

**Discussion:** In this multicenter prospective cohort, intraoperative systemic anticoagulation was not associated with a difference in rate of repair thrombosis or limb loss; but was associated with an increase in blood product requirements and prolonged hospital stay. Our data suggest there is no significant difference in outcome to support use of ISA for repair of traumatic arterial injuries.

**Keywords:** anticoagulation; trauma; vascular; extremity; amputation

## BACKGROUND

Routine intraoperative systemic anticoagulation (ISA) is a mainstay of therapy in elective arterial reconstruction and treatment of acute limb ischemia (1). In the setting of trauma, surgeons have been reluctant or unable to systemically anticoagulate patients when performing arterial repair due to concern for potential local and systemic bleeding (2). It is unclear if the improved patency seen with elective vascular repair can be generalized to traumatic arterial repair, particularly in patients with acute traumatic coagulopathy or resuscitation-associated coagulopathy. There is limited and conflicting retrospective data in the literature correlating improved patency or limb salvage with use of ISA during traumatic arterial injury repair (3-9). Retrospective reviews of patients who received ISA during lower extremity arterial injury repair report a limb salvage rate of 85-91% (2, 5, 7, 8). Other reviews, however, report lower limb salvage rates of 83-84% with similar injuries, despite routinely not giving ISA (4, 10). Comparative studies have shown no statistically significant difference in outcome between patients who are given ISA and those who are not (6, 7). Proponents, however, argue that the risks of ISA are minimal, and may decrease the risk of distal in situ thrombus or microvascular thrombosis (5, 9). We hypothesized that intraoperative systemic anticoagulation (ISA) decreased the risk of repair thrombosis or limb amputation (RTLA) after traumatic vascular injury of the extremities.

## METHODS

Patient data was collected from the American Association for the Surgery of Trauma (AAST) Multicenter PROspective Observational Vascular Injury Treatment (PROOVIT) registry. The details of this registry have been previously described (11). This is a

prospectively-collected database of injuries to named arterial and venous structures from fourteen Level I trauma centers across the United States. The database includes demographic, diagnostic, treatment, and outcome data for the index hospital stay. The registry is accruing data from clinic and readmission follow up.

Patients with upper or lower extremity arterial injuries who underwent open arterial revascularization between February 2013 and August 2015 were identified. Patients treated with arterial ligation, primary traumatic amputation, endovascular repair or embolization were excluded. Arterial injuries to the upper extremity utilized for analysis included individual injuries to the brachial or distal forearm arteries. The rare combined brachial and radial artery injuries were categorized as brachial artery injuries. Arterial injuries to the lower extremity included individual injuries to the femoral, popliteal or distal to the popliteal artery. Method of repair included autologous conduit, synthetic interposition or bypass graft and primary repair. Patients treated with vein interposition or bypass, vein patch or autologous artery as a conduit were included in the autologous category. ISA was defined as systemic anticoagulation with unfractionated heparin (UFH) utilized during the initial operation or vascular repair. Intraoperative regional anticoagulation was not included in this study. The total mangled extremity severity score (MESS) was calculated as originally described by Johansen et al., from the prospectively obtained components described in Appendix A (12).

The primary endpoint was a composite risk of RTLA during the index admission, between patients who did and did not undergo ISA during arterial injury repair. Secondary endpoints included need for reintervention after initial operation for any reason, total units of packed red blood cells (PRBC) required in the first 24 hours, length of intensive care unit (ICU) stay and length of total hospital stay.

Statistical analysis was performed using Stata Version 14.1 (StataCorp, College Station, TX, USA). Differences in demographics for patients who received ISA and were compared using the Wilcoxon rank-sum test for ordinal variables and two-sample t-test for continuous variables. The Fisher's exact test was used for 2x2 contingency tables with 20 or less patients in any category. P-values are reported as double the 1-sided exact probability. Pearson's chi-squared test with Yates' correction for continuity was used for 2x2 contingency tables when there were between 21 and 40 patients in a given category. Pearson's chi-squared test was used for all larger contingency tables. A p-value < 0.05 was considered statistically significant.

## RESULTS

Between February 2013 and August 2015, 193 patients with upper or lower extremity arterial injuries who underwent open arterial repair were entered into the PROOVIT registry from 14 Level-1 trauma centers. The 14 centers contributed between 1 and 52 patients each (mean 13.8, median 4), with five centers being the largest contributors with over 25 patients each. ISA was given to 119 patients in total (62%). The patients were predominantly male, with a mean age of 32.6 years (range 4-91, Table 1). Men were more likely to receive ISA than women (92% ISA were male vs. 78% without ISA were male,  $p = 0.02$ ). Most injuries were penetrating in nature (74%), and were most often caused by gunshot wounds (42%). The injury identified was most often a transection (63%). There were no differences in ISS, admission systolic blood pressure, or Glasgow coma score (GCS) between patients who received ISA and those who did not. There was a trend towards higher AIS-extremity in patients who received ISA compared to those who did not, but it did not reach statistical significance (median of 3 (25<sup>th</sup> percentile (Q1) - 75<sup>th</sup> percentile (Q3) 3-3) vs. 3 (Q1-Q3 2-3),  $p = 0.06$ ). MESS did not differ

between patients who received ISA than those who did not (median of 4 (Q1-Q3 3-6) vs. 4 (Q1-Q3 3-5),  $p = 0.08$ ). When each component was analyzed individually, however, patients who received ISA had a higher limb ischemia score compared to those who did not (median of 2 (Q1-Q3 1-2) vs. 1 (Q1-Q3 1-1),  $p < 0.001$ ).

In total, there were 71 concomitant venous injuries (37%), of which 63 were repaired (89%). The remaining 8 injured veins were ligated. Sixty-three patients had concomitant nerve injuries (33%), and 66 patients had associated orthopedic injury (34%). There were no significant differences in concomitant venous or orthopedic injuries between patients who received ISA and those who did not. Patients with concomitant nerve injuries were less likely to receive ISA (26% with ISA vs. 43% without,  $p = 0.02$ ).

Forty-three patients had a pre-hospital tourniquet placed (22%). Most patients had an ischemia time (from time of injury to time of definitive repair) between 3 and 6 hours (54%, Table 2). Damage-control temporary shunt placement was used in 9 patients (5%), 8 of whom received ISA. Arterial repair with autologous conduit was performed in 103 patients (53%), including 100 vein interposition or bypass grafts, 2 vein patches and one autologous artery used as conduit. The artery was repaired primarily in 81 patients (42%), and with synthetic graft in 8 patients (4%). Patients who underwent a repair with any autologous conduit were more likely to receive ISA than not (62% vs. 39%,  $p = 0.001$ ). Twenty-eight patients (15%) required a revision of the arterial repair during the initial operation (Table 2). There was no difference in administration of ISA in patients who required immediate revision (17% with ISA vs 11% without,  $p = 0.3$ ). Extremity fasciotomies were performed in 78 patients, including 13 involving the upper extremity. Patients who underwent fasciotomy at any time during the initial hospitalization were more likely to have received ISA than not (48% vs. 28%,  $p = 0.01$ ).

Patients who had an operative time of greater than 6 hours were more likely to receive ISA than not (10% vs. 5%,  $p = 0.04$ ).

There were 96 and 97 injuries to the upper and lower extremity, respectively. There were no combined upper and lower extremity injuries, and no combined above- and below-knee arterial injuries. There were two combined brachial and radial injuries. ISA was given for popliteal arterial injuries in 84% (26/31) of cases, in 67% (39/58) of femoral and in only 38% (3/8) of below-popliteal injuries ( $p < 0.001$ , Table 3). The total limb salvage rate was 94% (182/193). Popliteal artery injuries had the lowest rate of limb salvage (84%, 26/31). Lower extremity amputations were more frequent than upper extremity amputations (10% of lower extremity injuries (10/97) vs. 1.0% of upper (1/96),  $p = 0.005$ ). Rates of amputation and RTLA by artery injured and ISA status can be found in Table 3. Results were not analyzed for statistical significance given small numbers per group.

RTLA occurred in 22 patients (11%), including 11 amputations and 13 instances of graft thrombosis (Table 4). There was no significant difference in RTLA between patients who received ISA and those that did not (12/119 (10%) vs. 10/74 (14%),  $p = 0.6$ ).

There was significantly higher total blood product use among patients treated with ISA versus those that did not receive ISA (median 3 units (Q1-Q3 0-8) vs. 1 unit (Q1-Q3 0-4),  $p = 0.002$ ). There was a longer length of ICU (median 3 days (Q1-Q3 1-6) vs. 1 day (Q1-Q3 0-3),  $p = 0.001$ ) and hospital length of stay (median 9.5 days (Q1-Q3 4-18.5) vs. 6 days (Q1-Q3 2-13),  $p = 0.01$ ) in patients treated with ISA compared to those who were not. Nineteen patients required return to the operating room for reintervention during the index hospitalization (10%), including the 13 with repair thrombosis, one with hematoma, three with flow-limiting stenosis, one with a

pseudoaneurysm and one with an infection. There was no difference in need for reintervention between patients who underwent ISA and those who did not (9/119 (8%) vs. 10/74 (14%),  $p = 0.2$ ). There were no deaths or hemorrhagic strokes in the total cohort.

## DISCUSSION

Anticoagulation has been investigated as a modifiable risk factor to improve outcomes for patients with extremity arterial injuries. Early use of anticoagulation has been argued to minimize distal and small vessel thrombosis and therefore improve outflow patency (5, 9). Despite the dogma for using anticoagulation in vascular repair, in patients undergoing repair of traumatic vascular injuries there is minimal and conflicting data in the literature correlating the use of ISA with improved outcomes. Routine anticoagulation in the absence of contraindications has been recommended by multiple groups (5, 8, 9, 13), but has been found to have no difference by other groups (4, 6, 7, 10). Wagner et al. found a significantly lower amputation rate when ISA was used, in a review of 99 traumatic popliteal artery injuries (8% vs. 31%,  $p < 0.01$ ) (8). They did not, however, account for other confounding patient characteristics like degree of limb ischemia at presentation. Daugherty et al. compared patients with popliteal injuries who received ISA over two sequential five-year periods. Between 1967-1972, 13 patients received ISA with a limb salvage rate of 46%; in contrast to 7 patients who did not receive ISA and had a limb salvage rate of 43%. Between 1972-1977, 11 patients received ISA and the total limb salvage improved to 91% (5). They also report using improved operative techniques including extra-anatomic bypass in the latter time period, which could account for the difference in outcome. Melton et al. looked at 102 patients with popliteal artery injuries, 79% of whom were given ISA with or without thrombolysis (7). While there was a trend towards improved limb

salvage in patients treated with anticoagulation and/or thrombolysis compared to no treatment ( $p = 0.05$ ), there was no significant difference in limb salvage in subgroup of 46 patients who were given ISA alone ( $p = 0.19$ ) (7). Humphries et al. performed a modern retrospective review of 123 patients with extremity injuries, in which 56% of patients received ISA (6). They found no difference in RTLA with use of ISA (OR 0.74,  $p = 0.6$ ) (6). Similarly, we found no significant association between ISA and amputation and/or repair thrombosis.

The limb salvage rate observed in this study is consistent with modern studies (9), with 94% limb salvage. Popliteal artery injuries continue to have the poorest limb salvage rates. There is no appreciable improvement in the overall limb salvage rate of popliteal arteries since the 1980s; 84% in this modern study compared to historically reported rates of 83-100% (3-5, 7, 8, 13) despite improvements in hospital and pre-hospital care.

The biggest limitation of any database is the detailed information that are not collected. Specifically, data regarding other adjuvant anticoagulation strategies including use of local heparinized-containing irrigation intraoperatively, tranexemic acid, dextran, anticoagulation or antiplatelet agents given postoperatively, use of thrombectomy catheters, and details regarding specific ISA dose, pre- or post-administration activated clotting time levels were not collected in the PROOVIT database. These factors could be significant confounding variables and warrant further investigation.

One main reason anticoagulation is withheld during arterial repair for a trauma patient is the concern for bleeding complications due to concomitant injuries. Anticoagulation given to patients with traumatic arterial injuries without absolute contraindications has been reported to have no increase in the rate of bleeding complications (5, 6, 9, 10, 14). Wagner et al. found no

hemorrhagic complications in the 71 patients given intraoperative systemic anticoagulation (8). Humphries et al. found that use of ISA did not significantly change intraoperative blood loss (637 mL vs 926 mL,  $p = 0.23$ ) or overall bleeding complications (42% vs 45%,  $p = 0.95$ ) (6). Golob et al. found a total complication (major and minor) rate of 21% in 114 patients given anticoagulation after traumatic injury (15). Our study found significantly higher total PRBC use in patients receiving ISA, as well as longer hospital and ICU stays despite similar ISS, MESS and GCS between the groups. However, the outcomes of thrombosis, amputation, stroke or death were unchanged between the groups. The PROOVIT database does not currently include data regarding specific bleeding complications or strict contraindications for anticoagulation (i.e. intra-cavitary hemorrhage, need for multiple operations), and therefore these potential confounders will be missed.

Though prospectively obtained, this database reflects modern practice only among major Level I academic institutions across the country. Practice patterns of the 5 centers with higher enrollment may dictate some of the trends observed. The database did not collect information on the level of training or specialty of the operating surgeon. This study focused on open arterial repairs, as there were only two identified endovascular repairs undertaken for extremity arterial trauma recorded in the PROOVIT database for this time period. Use and outcomes of endovascular techniques for extremity trauma is being actively explored (16, 17), but outcomes associated with these technologies will require additional investigation as experience matures. This preliminary report focuses on in-hospital outcomes following traumatic arterial injury repair, and does not include delayed amputations that may be required long term for limb dysfunction, delayed repair thrombosis or infection. A power calculation determined that to detect a 3% difference in rate of amputation, 1496 total patients should be analyzed. A more

robust data set with information on outcomes will be obtained as the PROOVIT database continues to mature.

In this study, anticoagulation given during an operation was not associated with improved graft patency or limb salvage. Furthermore, ISA use was associated with prolonged hospital stay and increased blood product use. Our data suggest that for traumatic arterial injuries, there is no significant difference in outcome to support use of ISA. Further investigation regarding the risks of ISA for traumatic vascular injuries is needed.

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Table 1: Demographics of included patients, analyzed by intraoperative anticoagulation status.

Factor	All	Intraoperative Systemic Anticoagulation		p-value
		Received	Not Received	
Mean age (SD)	32.6 (15.3)	32.2 (15.1)	33.4 (15.7)	0.6*
Male, n (%)	167/193 (87)	109/119 (92)	58/74 (78)	0.02†
Injury mechanism				0.5†
Blunt, n (%)	47/193 (24)	32/119 (27)	15/74 (20)	
Penetrating, n (%)	142/193 (74)	85/119 (71)	57/74 (77)	
Mixed blunt and penetrating, n (%)	4/193 (2)	2/119 (2)	2/74 (3)	
Specific mechanism				0.5†
Gunshot, n (%)	80/193 (42)	53/119 (45)	27/74 (37)	
Stabbing, n (%)	29/193 (15)	16/119 (13)	13/74 (18)	
Motor Vehicle Collision, n (%)	25/193 (13)	17/119 (14)	8/74 (11)	
Other, n (%)	59/193 (31)	33/119 (28)	26/74 (35)	
Injury description				0.5†
Flow limiting defect, n (%)	33/193 (17)	22/119 (19)	11/74 (15)	
Occlusion, n (%)	24/193 (12)	18/119 (15)	6/74 (8)	
Pseudoaneurysm, n (%)	6/193 (3)	3/119 (3)	3/74 (4)	
Transection, n (%)	121/193 (63)	71/119 (60)	50/74 (68)	
Other injury type, n (%)	9/193 (5)	5/119 (4)	4/74 (5)	
Median ISS (Q1, Q3)	9 (9, 16)	10 (9, 16)	9 (5, 16)	0.1§
Mean admission SBP (SD)	120.9 (28.5)	120.5 (29.8)	121.6 (26.6)	0.8*
Median GCS (Q1, Q3)	15 (15, 15)	15 (15, 15)	15 (15, 15)	0.7§
Median AIS-extremity (Q1, Q3)	3 (3, 3)	3 (3, 3)	3 (2, 3)	0.06§
Median MESS (Q1, Q3)	4 (3, 6)	4 (3, 6)	4 (3, 5)	0.08§
Median Skeletal / Soft tissue Score (Q1, Q3)	1 (1, 2)	1 (1, 2)	1 (1, 1)	0.1§
Median Limb Ischemia Score (Q1, Q3)	1 (1, 2)	2 (1, 2)	1 (1, 1)	< 0.001§
Median Shock Score (Q1, Q3)	0 (0, 1)	0 (0, 1)	0 (0, 1)	0.9§
Median Age Score (Q1, Q3)	0 (0, 1)	0 (0, 1)	1 (0, 1)	0.3§
Concomitant vein injury, n (%)	71/193 (37)	44/119 (37)	27/74 (37)	0.9‡
Vein repaired, n (%)	63/71 (89)	40/44 (91)	23/27 (85)	0.7‡
Concomitant nerve injury, n (%)	63/193 (33)	31/119 (26)	32/74 (43)	0.02‡
Concomitant orthopedic injury, n (%)	66/193 (34)	43/119 (36)	23/74 (31)	0.6‡

\* Two-tailed t-test

† Pearson's Chi-square

‡ Chi-square with Yates' continuity correction

§ Wilcoxon Rank-Sum

ISS = Injury severity score

AIS = Abbreviated injury score

SBP = Systolic blood pressure

GCS = Glasgow coma score

MESS = Mangled extremity severity score

SD = standard deviation

Q1 = Lower quantile (25<sup>th</sup> percentile)Q3 = Upper quantile (75<sup>th</sup> percentile)

Table 2: Management of injuries, analyzed by intraoperative anticoagulation status.

Factor	All	Intraoperative Systemic Anticoagulation		p-value
		Received	Not Received	
Pre-hospital Tourniquet, n (%)	43/193 (22)	24/119 (20)	19/74 (26)	0.4
Time from Injury to Repair				0.4†
Less than 3 hours, n (%)	41/193 (21)	23/119 (19)	18/74 (24)	
3 - 6 hours, n (%)	104/193 (54)	71/119 (60)	33/74 (45)	
Greater than 6 hours, n (%)	33/193 (17)	20/119 (17)	13/74 (18)	
Temporary shunt utilized, n (%)	9/193 (5)	8/119 (7)	1/74 (1)	0.2
Repair Method				0.001†
Autologous repair, n (%)	103/193 (53)	74/119 (62)	29/74 (39)	
Primary repair, n (%)	81/193 (42)	38/119 (32)	43/74 (58)	
Synthetic graft utilization, n (%)	8/193 (4)	7/119 (6)	1/74 (1)	
Immediate revision required intraoperatively, n (%)	28/193 (15)	20/119 (17)	8/74 (11)	0.3
Fasciotomy, n (%)	78/193 (40)	57/119 (48)	21/74 (28)	0.01‡
Intraoperative time				0.04†
Less than 3 hours, n (%)	78/193 (40)	42/119 (35)	36/74 (49)	
3 - 6 hours, n (%)	84/193 (44)	60/119 (50)	24/74 (32)	
Greater than 6 hours, n (%)	16/193 (8)	12/119 (10)	4/74 (5)	

† Pearson's Chi-square

‡ Chi-square with Yates' continuity correction

1-tailed Fisher's exact test, doubled

Table 3: Analysis of intraoperative anticoagulation status and outcome, by artery injured.

Artery Injured	Total Injuries	ISA Received	Amputations		RTLAs	
			ISA Received	ISA Not Received	ISA Received	ISA Not Received
Brachial artery, n (%)	47/193 (24)	32/47 (68)	0/32 (0)	0/15 (0)	3/32 (9)	2/15 (13)
Forearm arteries, n (%)	49/193 (25)	19/49 (39)	1/19 (5)	0/30 (0)	1/19 (5)	1/30 (3)
Femoral artery, n (%)	58/193 (30)	39/58 (67)	2/39 (5)	2/19 (11)	4/39 (10)	3/19 (16)
Popliteal artery, n (%)	31/193 (16)	26/31 (84)	4/26 (15)	1/5 (20)	4/26 (15)	3/5 (60)
Distal to popliteal, n (%)	8/193 (4)	3/8 (38)	0/3 (0)	1/5 (20)	0/3 (0)	1/5 (20)

RTLA = Repair thrombosis and / or amputation

ISA = intraoperative systemic anticoagulation

Table 4: Outcomes after repair, analyzed by intraoperative anticoagulation status.

Outcome	Total	Intraoperative systemic anticoagulation		p-value
		Received	Not received	
Median total units PRBC (Q1, Q3)	2 (0, 6)	3 (0, 8)	1 (0, 4)	0.002 <sup>§</sup>
Median days of ICU stay (Q1, Q3)	2 (0, 5)	3 (1, 6)	1 (0, 3)	0.001 <sup>§</sup>
Median days of total hospital stay (Q1, Q3)	8 (3, 17)	9.5 (4, 18.5)	6 (2, 13)	0.01 <sup>§</sup>
Re-intervention required after repair, n (%)	19/193 (10)	9/119 (8)	10/74 (14)	0.2
Composite endpoint RTLA, n (%)	22/193 (11)	12/119 (10)	10/74 (14)	0.6
Amputation, n (%)	11/193 (6)	7/119 (6)	4/74 (5)	1.0
Thrombosis, n (%)	13/193 (7)	6/119 (5)	7/74 (10)	0.4

<sup>§</sup> Wilcoxon Rank-Sum

1-tailed Fisher's exact test, doubled

RTLA = Repair thrombosis and / or amputation

PRBC = Packed red blood cells

ICU = intensive care unit

Q1 = Lower quantile (25<sup>th</sup> percentile)

Q3 = Upper quantile (75<sup>th</sup> percentile)