Noniatrogenic spinal cord ischemia: A patient level meta-analysis of 125 case reports and series

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ABSTRACT

Background: Guidelines are needed to manage spinal cord infarctions. Here, we evaluated the incidence of noniatrogenic spinal ischemia, focusing on the spinal levels involved, and the relative efficacy of different management strategies.

Methods: We performed a meta-analysis of 147 patients who sustained noniatrogenic spinal cord ischemia within the past 10 years. The most common causes of injury were idiopathic (i.e., 47% medical/surgery-related) followed by systemic/chronic conditions (23.6%) and aortic vascular pathology (20%). Postdiagnostic treatment options included rehabilitation in 53.7% of patients, while steroids (35.37%), antiplatelets aggregates (30.61%), and anticoagulation (18.37%) were also used.

Results: Traumatic causes of spinal cord ischemia were associated with worse outcomes, while those without a clear diagnosis despite extensive work-up had better results. At discharge, patients managed with cerebrospinal fluid (CSF) drainage had significant improvement (\( P = 0.04 \)), while other therapies were not effective. Notably, ischemia mostly occurring between the T4 and T7 levels and was associated with the worst outcomes. In this thoracic "watershed" region, thoracic cord ischemia was most likely attributed to an increased susceptibility to cord under-perfusion in this region (\( P < 0.05 \)).

Conclusion: This meta-analysis revealed a variety of etiologies for noniatrogenic typically T4-T7 spinal cord ischemia. Several different treatment strategies may be utilized in this patient population, including CSF drainage, blood pressure elevation, corticosteroids, antiplatelets/anticoagulants/thrombolytics, mannitol, naloxone, surgical revascularization, hyperbaric oxygen, and systemic hypothermia.

Keywords: Cerebrovascular accident, Iatrogenic injury, Spinal infarction, Spinal cord injury, Stroke

INTRODUCTION

The incidence of spinal cord infarction is approximately 0.003%.[⁹] Spinal cord ischemia (SCI) is variously attributed to aortic, surgery, or injury (i.e., most commonly due to medical/surgical procedures). Specifically, noniatrogenic SCI may be due to trauma, arteriosclerosis, spinal vascular pathologies (i.e., arteriovenous malformations and thrombotic/fibrocartilaginous emboli), chronic conditions (i.e., polycythemia vera), mechanical strain (i.e., vertebral hyperextension), transverse myelitis, infection, and/or neoplasm.⁴,⁵ Notably, initial magnetic resonance imaging may be normal as it may take several days for SCI to appear on these studies.⁶ The treatments...
for noniatrogenic SCI/stroke include cerebrospinal fluid (CSF) drainage, blood pressure elevation, corticosteroids, antiplatelets/anticoagulants/thrombolytics, mannitol, naloxone, surgical revascularization, hyperbaric oxygen (HBO), and systemic hypothermia.\cite{1,4} Here, we stratified the various etiologies and treatments available for treating noniatrogenic SCI, and correlated them with patient outcomes.

MATERIALS AND METHODS

This systematic review was undertaken and reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines [Figure 1].\cite{6}

Eligibility criteria and search strategies

We gathered information on the management of spinal ischemia in 147 patients over the past 10 years. Eligibility criteria were defined before the literature search [Table 1]. Case reports/series were identified through an exhaustive search on PUBMED and MEDLINE, using the search: “spinal cord ischemia,” or “spinal cord infarction,” or “spinal cord stroke.” Only the articles adherent to CARE guidelines for involving 147 patients were included in the study.

Clinical data

The 147 patients included in this analysis averaged 45 years of age; 55.4% were male. Ischemic SCI injuries were classified as idiopathic (classified because of unknown etiology, 47.3%), 23.6% systemic or chronic conditions (e.g., polycythemia vera), and 19.6% due to aortic/vascular pathology. Noniatrogenic ischemic SCI resulted in the following deficits: motor (146), sensory (125), and autonomic impairment (i.e., 59% including loss of bowel and bladder functional). The American Spinal Injury Association (ASIA) scores were used to classify most patients’ neurological function following noniatrogenic SCI and included; A – (37.8%), D – (22.3%); with A- and B-level impairment being critical (58%), while B- and C-level impairment was subcritical (42%) [Supplemental Table 1 and Supplemental Figure 1]. Outcomes were scored from −2 to 3, with −2 being patient death and 3 being complete recovery of patients [Supplemental Table 2].

Summary measures and statistical analysis

Data analysis was performed using GraphPad Prism 9.0 (GraphPad Software, Inc., San Diego, CA) and MATLAB 2020b (MathWorks, Inc., Natick, MA) software. We also used Fisher’s exact test or Chi-goodness-of-fit test, odds ratios, the Haldane-Anscombe correction, and the Cochran-Mantel-Haenszel test which were utilized.

RESULTS

Therapeutic management of infarctions

Following the PRISMA guidelines, we utilized 125 records, involving a total of 147 total patients, sustaining noniatrogenic spinal cord ischemic injuries [Figure 1, Tables 2 and 3]. Various strategies were used to manage noniatrogenic spinal cord injury; rehabilitation (53.7%), medical therapy/steroids (35.37%), antiplatelet aggregates (i.e., aspirin and clopidogrel...
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Table 1: Eligibility criteria.

| Inclusion | Exclusion |
|-----------|-----------|
| Case reports or series with spinal ischemia published between 2010 and 2020 | No information on ASIA scale impairment or insufficient evidence |
| Noniatrogenic injury | Ambiguous language on management |
| Discharge status or follow-up outcome |

ASIA: American Spinal Injury Association

Table 2: Summary statistics.

| Feature | μ (σ) | Range (%) |
|---------|-------|-----------|
| Age     | 45.025 (23.0) | 0.67–85 |
| Features | # of patients | % of patients |
| Sex | | |
| Male | 81 | 55.41 |
| Females | 65 | 43.92 |
| Unknown | 1 | 0.68 |
| Features: exciting factors | | |
| Idiopathic | 70 | 47.30 |
| Hypotension/shock mediated | 9 | 6.08 |
| Trauma | 11 | 7.43 |
| Thromboembolic | 26 | 17.69 |
| Aortic vascular pathology | 28 | 19.59 |
| Spinal vascular pathology | 8 | 5.41 |
| Compressive/mechanical | 25 | 16.89 |
| Systemic/chronic condition | 35 | 23.65 |

[30.61%]), or anticoagulation (i.e., heparin and warfarin [18.37%]). In addition, a few patients utilized; HBO (two patients), edaravone (three patients), or hypothermia (one patient). Surgery in 25 patients included seven endovascular procedures and four laminectomies/discectomies, while other surgical management was heterogeneous (i.e., including open surgical management) [Supplemental Table 3].

Outcomes

Of the 147 patients’ outcomes that were analyzed those with spinal cord ischemia due to trauma or systemic/chronic causes had poor overall outcomes, while those presenting with idiopathic causes or aortic vascular pathologies had improved outcomes [Figures 2 and 3]. Only CSF drainage was associated with improved outcomes, while those using antiplatelet therapy trended toward improved outcomes. Steroids were significantly associated with no improvement/worsening. Further, overall outcomes were worse for patients with severe ASIA (i.e., A- and B-level) impairment following injury. Except for patients ages 8–30 who demonstrated significantly poorer outcomes at follow-up, age and sex were not associated with overall poorer outcomes.

Table 3: Clinical features of patients.

| Features: grade of disability | 146 | 99.32% |
| Motor impairment | 125 | 85.14% |
| Sensory impairment | 87 | 59.46% |
| Autonomic impairment | 55 | 37.84% |
| ASIA A | 30 | 20.27% |
| ASIA B | 29 | 19.59% |
| ASIA D | 33 | 22.30% |
| ASIA E | 0 | 0.00% |
| Patients with known spinal level | 132 | 89.86% |
| Features: treatment measures | | |
| Anticoagulation | 27 | 18.37% |
| Antiplatelets | 45 | 30.61% |
| BP management | 18 | 12.24% |
| Mannitol | 2 | 1.36% |
| Naloxone | 0 | 0.00% |
| Steroids | 52 | 35.37% |
| CSF drainage | 11 | 7.48% |
| Thrombolytics | 5 | 3.40% |
| Therapeutic surgical intervention | 25 | 17.01% |
| Endovascular revascularization | 7 | 4.76% |
| Rehab | 79 | 53.74% |
| Hyperbaric oxygen | 2 | 1.36% |
| Hypothermia | 1 | 0.68% |
| Edaravone | 3 | 2.04% |

ASIA: American Spinal Injury Association, CSF: Cerebrospinal fluid, BP: Blood pressure

Associations with location of infarctions

The level of ischemic cord injury correlated with the level of spinal infarction [Figure 4a]. Locations of SCI included the cervical (C), upper thoracic (T1-T6, UT), lower thoracic (T7-T12, LT), and lumbar (L) regions [Figures 4b and c]. There was a higher frequency of cervical and lower thoracic cord injuries, with the most severe injuries occurring in the upper thoracic region (i.e., patients with T4-T6 ischemia were significantly less likely to improve). Patients without autonomic symptoms presented with significantly higher rates of infarction in the following regions cervical (C1-C3), upper thoracic (T6-T7), and T10-conus regions. Those without sensory impairment had more cervical infarctions localized to the upper cervical (C2-C3) and lower thoracic levels.

Emerging therapeutics

Emerging therapies for ischemic SCI included the use of statins, edaravone, and HBO, and selective surgery. Those undergoing aortic aneurysm repair following ischemia and experienced some improvement. However, the four patients were surgically revascularized (i.e., stent or bypass) and demonstrated no significant improvement
For six patients undergoing discectomies, laminectomies, or laminoplasties, four improved, one remained unchanged, while one was worse [Tables 4 and 5].

| Total Outcomes  | Discharge Outcomes  | Follow-up Outcomes  |
|-----------------|---------------------|---------------------|
| Systemic/Chronic Conditions | 0.523 [0.228,1.200] | 0.410 [0.178,0.982] | 0.607 [0.205,1.797] |
| Compressive Pathologies | 0.506 [0.201,1.370] | 0.756 [0.287,1.987] | 0.562 [0.175,1.801] |
| Spinal Vascular Pathologies | 2.356 [0.280,19.824] | 2.069 [0.384,11.144] | 2.667 [0.152,53.688] |
| Aortic Vascular Pathologies | 1.621 [0.567,4.831] | 2.857 [1.095,7.454] | 3.836 [0.475,30.955] |
| Thromboembolic Disease | 0.677 [0.260,1.724] | 0.670 [0.275,1.633] | 1.250 [0.326,4.768] |
| Trauma | 0.236 [0.067,0.827] | 0.307 [0.075,1.256] | 0.366 [0.069,1.672] |
| Hypotension/Shock | 2.718 [0.328,22.511] | 0.450 [0.102,1.982] | 1.750 [0.203,15.051] |
| Idiopathic | 2.189 [0.997,4.867] | 1.279 [0.600,2.714] | 1.719 [0.657,5.502] |

Table 4: Outcomes of emerging therapies.

| Treated with | Patient # | ASIA score | Death | Worsened | No change | Some improvement | Mostly improved | Full improvement |
|--------------|-----------|------------|-------|----------|-----------|-----------------|----------------|-----------------|
| HBO         | 1 C       | x          |       |          |           |                 |                 |                 |
|             | 2 A       | x          |       |          |           |                 |                 |                 |
| Statin      | 1 B       | x          |       | x        |           |                 |                 |                 |
|             | 2 D       | x          |       |          |           |                 |                 |                 |
|             | 3 D       | x          |       |          |           |                 |                 |                 |
|             | 4 D       | x          |       |          |           |                 |                 |                 |
|             | 5 B       | x          |       |          |           |                 |                 |                 |
|             | 6 A       | x          |       | x        |           |                 |                 |                 |
| Edaravone   | 1 A       | x          |       | x        |           |                 |                 |                 |
|             | 2 A       | x          |       |          |           |                 |                 |                 |
|             | 3 C       | x          |       |          |           |                 |                 |                 |

HBO: Hyperbaric oxygen, ASIA: American Spinal Injury Association
Figure 3: Forest plots of outcomes in noniatrogenic spinal infarctions by (a) severity of injury and (b) reported patient demographics. Significance determined by $P < 0.05$ and denoted by asterisk (*).

Table 5: Outcomes for surgical intervention.

| Type of surgery                  | Patient | ASIA score | Death | Worsened | No change | Some improvement | Mostly improved | Full improvement |
|----------------------------------|---------|------------|-------|----------|-----------|------------------|-----------------|-----------------|
| Aneurysm repair                  | 1 B     | x          |       |          |           |                  |                 |                 |
|                                  | 2 B     |            |       |          | x         |                  |                 |                 |
|                                  | 3 A     | x          |       |          |           |                  |                 |                 |
| Removal of pathology             | 1 A     | x          |       |          |           |                  |                 |                 |
| (tumor, AVM, and hematoma)       | 2 C     |            |       |          | x         |                  |                 |                 |
|                                  | 3 D     | x          |       |          |           |                  |                 |                 |
| Discectomy/laminectomy/laminoplasty | 1 B    | x          |       |          |           |                  |                 |                 |
|                                  | 2 A     |            |       |          | x         |                  |                 |                 |
|                                  | 3 C     | x          |       |          |           |                  |                 |                 |
|                                  | 4 A     | x          |       |          |           |                  |                 |                 |
|                                  | 5 D     | x          |       |          |           |                  |                 |                 |
|                                  | 6 A     | x          |       |          |           |                  |                 |                 |
| Revascularization (stent or bypass) | 1 D    | x          |       |          |           |                  |                 |                 |
|                                  | 2 A     | x          |       |          |           |                  |                 |                 |
|                                  | 3 C     | x          |       |          |           |                  |                 |                 |
|                                  | 4 D     | x          |       |          |           |                  |                 |                 |

ASIA: American Spinal Association Injury, AVM: Arteriovenous malformations
DISCUSSION

Here, we performed a meta-analysis of 125 case reports involving 147 patients to evaluate the incidence of noniatrogenic spinal cord ischemia, focusing on causes, treatment, and outcomes.\textsuperscript{7,10-12} The severity of ischemic injury proved predictive for worst outcomes for all SCI. Further, those with ASIA A- and B-level (i.e., ischemic infarction more commonly found in lower thoracic and lumbar levels) injuries had poorer outcomes, while those with ASIA C-level impairment had significantly better results.\textsuperscript{8} Further, lower thoracic and lumbar ischemia was also significantly associated with autonomic impairment (i.e.,

Figure 4: Association with location of injury with outcomes. (a) Association of location with normalized frequency of patient demographics. (b) Association of location by etiology of injury and (c) age and injury severity. Significance determined by $P < 0.05$ and denoted by asterisk (*). Trend toward significance determined by $P < 0.10$ and denoted by (#).
consistent with T10-L3 location of sympathetic efferent fibers to the bowel and bladder).\(^{(13)}\)

**CONCLUSION**

Based on a meta-analysis of 147 patients, effective strategies for treating noniatrogenic spinal cord injury included predominantly CSF drainage and antiplatelet aggregate therapy and, while other treatment options (i.e., steroid usage, HBO, and edaravone) were less effective.

**Declaration of patient consent**

Patient’s consent not required as there are no patients in this study.

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Nil.

**Conflicts of interest**

There are no conflicts of interest.

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**SUPPLEMENTAL FIGURE**

Supplemental Figure 1: A comparison of ASIA impairment to the categorical dysfunction. Motor (M), sensory (S), autonomic (A), dysfunction compared to ASIA-A through ASIA-D. Autonomic dysfunction is present most frequently in ASIA-A impairment. Sensory impairment is also present most frequently in ASIA-A. About 70% of ASIA-A have motor, sensory, and autonomic impairment.
### SUPPLEMENTAL TABLES

#### Supplemental Table 1: ASIA impairment scale.

| ASIA | Severity       | Description                                                                                   |
|------|----------------|----------------------------------------------------------------------------------------------|
| A    | Complete       | No motor or sensory function is preserved in the sacral segments S4-S5                      |
| B    | Sensory incomplete | Sensory but not motor function is preserved below the neurological level and includes the sacral segments S4-S5 and no motor function is preserved more than 3 levels below the motor level on either side of the body |
| C    | Motor incomplete | Motor function is preserved below the neurological level and more than half of key muscles below the neurological level have a muscle grade of 3 |
| D    | Motor incomplete | Motor function is preserved below the neurological level, and at least half of key muscles below the neurological level have a muscle grade of 3 or more |
| E    | Normal         | Motor and sensory function are normal                                                        |

#### Supplemental Table 2: Outcome scale.

| Score | Significance                                                                                     |
|-------|--------------------------------------------------------------------------------------------------|
| –2    | Patient death                                                                                    |
| –1    | Worsening in patient symptoms compared to initial presentation                                 |
| 0     | No change in patient symptoms compared to initial presentation                                  |
| 1     | Mild improvement in patient symptoms compared to initial presentation                           |
| 2     | Substantial to nearly complete improvement in patient symptoms compared to initial presentation |
| 3     | Complete recovery to patient baseline compared to initial symptoms                              |

#### Supplemental Table 3: Surgical intervention counts.

| Type of surgery                                | Number of patients |
|------------------------------------------------|--------------------|
| Aneurysm repair                                | 3                  |
| Removal of pathology (tumor, AVM, and hematoma) | 4                  |
| Revascularization                              | 7                  |
| Discectomy/laminectomy/laminoplasty            | 4                  |
| Other                                          | 7                  |
### Supplemental Table 4: Subgroup analysis.

| Outcome measure | Management | Idiopathic | Hypotension | Trauma | Thromboembolic |
|-----------------|------------|------------|-------------|--------|----------------|
|                  |            |            |             |        |                |
|                  |            | 1.154 (0.034–38.880), P=0.94 | 0.333 (0.011–10.108), P=0.53 | 3.500 (0.346–35.371), P=0.37 |
| Total outcomes   | Anticoagulation | 1.444 (0.281–7.438), P=1.00 | 1.154 (0.034–38.880), P=0.94 | 1.182 (0.020–69.981), P=0.94 |
|                  | Antiplatelet | 1.219 (0.346–4.291), P=1.00 | 1.250 (0.058–26.869), P=1.00 | 1.514 (0.172–7.745), P=1.00 |
|                  | BP control   | 0.393 (0.033–4.719), P=0.44 | 0.667 (0.060–7.352), P=1.00 | 0.875 (0.068–11.313), P=1.00 |
|                  | Steroids     | 1.137 (0.332–4.006), P=1.00 | 4.333 (0.142–132.324), P=0.40 | 2.576 (0.111–59.938), P=0.56 |
|                  | CSF drain    | 0.214 (0.004–11.291), P=0.45 | 1.375 (0.022–6.348), P=1.00 | 0.833 (0.147–4.723), P=1.00 |
|                  | All surgical int. | 1.106 (0.050–24.497), P=0.95 | 1.909 (0.059–61.347), P=0.71 | 0.943 (0.092–2.730), P=0.66 |
|                  | Endovascular int. | 0.652 (0.025–16.965), P=0.80 | 0.600 (0.016–23.069), P=0.78 | 0.176 (0.026–29.039), P=0.94 |
|                  | Rehab        | 0.943 (0.268–3.332), P=1.00 | 0.867 (0.060–7.352), P=1.00 | 0.500 (0.092–2.730), P=0.66 |
| Discharge outcomes | Anticoagulation | 1.147 (0.323–6.766), P=0.72 | 2.000 (0.077–51.593), P=1.00 | 0.619 (0.020–19.586), P=0.79 |
|                  | Antiplatelet | 1.426 (0.423–4.808), P=0.76 | 2.143 (0.035–131.942), P=0.72 | 3.333 (0.599–18.543), P=0.23 |
|                  | BP control   | 0.321 (0.027–3.809), P=0.56 | 3.000 (0.122–73.642), P=1.00 | 4.333 (0.017–65.963), P=0.83 |
|                  | Steroids     | 2.872 (0.861–9.575), P=0.14 | 1.571 (0.025–98.963), P=0.83 | 0.333 (0.017–65.963), P=0.83 |
|                  | CSF drain    | 0.695 (0.013–36.465), P=0.86 | 9.000 (0.270–299.879), P=0.22 | 1.000 (0.270–299.879), P=0.22 |
|                  | All surgical int. | 3.727 (0.170–81.899), P=0.40 | 77.000 (1.223–4849.190), P=0.04 | 1.000 (0.270–299.879), P=0.22 |
|                  | Endovascular int. | 2.158 (0.084–55.687), P=0.64 | 6.600 (0.193–225.808), P=0.30 | 7.727 (0.150–39.853), P=0.19 |
|                  | Rehab        | 1.219 (0.384–3.872), P=0.78 | 0.500 (0.019–12.898), P=1.00 | 1.143 (0.230–5.670), P=1.00 |
| Follow-up outcomes | Anticoagulation | 1.800 (0.199–16.262), P=1.00 | 1.364 (0.040–46.655), P=0.86 | 3.667 (0.159–84.519), P=0.42 |
|                  | Antiplatelet | 1.018 (0.244–4.257), P=1.00 | 1.364 (0.040–46.655), P=0.86 | 10.321 (0.449–233.245), P=0.14 |
|                  | BP control   | 0.588 (0.022–15.544), P=0.75 | 0.692 (0.018–26.907), P=0.84 | 2.333 (0.071–76.670), P=0.63 |
|                  | Steroids     | 0.862 (0.206–3.613), P=1.00 | 0.862 (0.018–26.907), P=0.84 | 3.755 (0.022–63.48), P=0.14 |
|                  | CSF drain    | 0.192 (0.004–10.281), P=0.42 | 1.364 (0.040–46.655), P=0.46 | 0.333 (0.017–65.963), P=1.00 |
|                  | All surgical int. | 1.000 (0.044–22.540), P=1.00 | 1.498 (0.032–46.575), P=0.46 | 0.727 (0.051–10.390), P=1.00 |
|                  | Endovascular int. | 0.588 (0.022–15.544), P=0.75 | 0.692 (0.018–26.907), P=0.84 | 0.727 (0.051–10.390), P=1.00 |
|                  | Rehab        | 0.351 (0.066–1.861), P=0.28 | 0.733 (0.021–25.090), P=0.86 | 0.333 (0.017–65.963), P=1.00 |

(Contd...)
Supplemental Table 4: (Continued)

| Outcome measure | Management | Aortic vascular pathology | Spinal vasc. pathology | Compressive | Systemic/chronic |
|-----------------|------------|---------------------------|------------------------|-------------|------------------|
| Follow-up outcomes | Anticoagulation | 0.913 (0.030–27.828), P=0.96 | 0.333 (0.004–25.409), P=0.62 | 2.391 (0.097–58.778), P=0.59 | 4.333 (0.202–93.159), P=0.35 |
| Follow-up outcomes | Antiplatelet | 0.333 (0.009–12.421), P=0.55 | 0.333 (0.004–25.409), P=0.62 | 3.667 (0.159–84.519), P=0.42 | 0.833 (0.114–6.111), P=1.00 |
| Follow-up outcomes | BP control | 1.286 (0.043–37.983), P=0.88 | 0.091 (0.001–11.885), P=0.33 | 1.320 (0.046–37.779), P=0.87 | 2.097 (0.088–49.996), P=0.65 |
| Follow-up outcomes | Steroids | 0.011 (0.000–0.818), P=0.04 | 0.091 (0.001–11.885), P=0.33 | 0.400 (0.034–4.681), P=0.61 | 0.133 (0.015–1.176), P=0.09 |
| Follow-up outcomes | CSF drain | 2.294 (0.080–66.022), P=0.63 | 0.091 (0.001–11.885), P=0.33 | 0.111 (0.004–3.243), P=0.20 | 2.097 (0.088–49.996), P=0.65 |
| Follow-up outcomes | All surgical int. | 2.294 (0.080–66.022), P=0.63 | 0.714 (0.010–49.712), P=0.88 | 3.667 (0.159–84.519), P=0.42 | 2.097 (0.088–49.996), P=0.65 |
| Follow-up outcomes | Endovascular int. | 0.600 (0.018–19.414), P=0.77 | 0.091 (0.001–11.885), P=0.33 | 0.407 (0.007–23.231), P=0.66 | 1.182 (0.042–32.915), P=0.92 |
| Follow-up outcomes | Rehab | 0.255 (0.009–7.336), P=0.43 | 1.400 (0.020–97.435), P=0.88 | 0.400 (0.034–4.681), P=0.61 | 0.700 (0.108–4.538), P=1.00 |