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Original Article

Intra-Arterial Papaverine Used to Treat Cerebral Vasospasm Reduces Brain Oxygen

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Abstract

Introduction: Intra-arterial papaverine (IAP) is used to treat symptomatic cerebral vasospasm following aneurysmal subarachnoid hemorrhage (SAH). IAP, however, can increase intracranial pressure (ICP). In this study we examined whether IAP alters brain oxygen (BtO_2).

Methods: Poor clinical grade (Hunt & Hess IV or V) SAH patients who underwent continuous ICP and BtO_2 monitoring during IAP infusion for symptomatic cerebral vasospasm were evaluated as part of a prospective observational study.

Results: Data are available for five patients (median age 58) who received IAP for cerebral vasospasm 4 to 7 days after SAH. In each patient, angiographic vasospasm was improved on postinfusion angiogram. Mean ICP before IAP was 23.04 ± 1.18 mmHg; it increased immediately after IAP infusion and remained elevated (29.89 ± 1.18 mmHg; $p < 0.05$) during IAP and for approximately 10 minutes after IAP ended. Baseline mean arterial pressure (MAP) was 110.55 ± 1.36 mmHg. During IAP treatment MAP remained stable (110.90 ± 2.00 mmHg; $p = 0.31$). Mean BtO_2 before IAP was 32.99 ± 1.45 mmHg. There was a significant BtO_2 decrease in all patients during IAP to a mean of 22.96 ± 2.9 mmHg ($p < 0.05$). BtO_2 returned to baseline within 10 minutes after IAP ended. There was a modest relationship between the ICP increase and BtO_2 decrease ($R^2 = 0.526$).

Conclusion: IAP infusion to treat cerebral vasospasm following SAH can increase ICP and reduce BtO_2. The IAP-induced reduction in BtO_2 may help explain why IAP, although it reverses arterial narrowing, does not improve patient outcome.

Key Words: Brain oxygen; intra-arterial papaverine; subarachnoid hemorrhage; vasospasm; intracranial pressure.

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Introduction

Cerebral vasospasm is a frequent complication and a leading cause of preventable morbidity and mortality after aneurysmal subarachnoid hemorrhage (SAH; *1*). Despite extensive research, an effective therapy to prevent or treat vasospasm and its clinical consequences remains elusive. Early aneurysm occlusion, calcium (Ca^{2+}) channel blockers, and careful fluid management are most frequently used to manage vasospasm *(1)*. When patients remain refractory to maximal medical measures, endovascular strategies such as balloon angioplasty or intra-arterial administration of papaverine (IAP) are used at many cerebrovascular centers *(2)*. Both techniques successfully dilate

vasospastic arteries. The clinical outcome of IAP, however, is less certain than that associated with balloon angioplasty *(2–10)*. The reasons for this are unclear but may be associated with IAP's adverse effects on intracranial pressure (ICP), blood pressure *(4,11)*, or IAP-preservative toxicity *(12)*.

Increased ICP is common finding after SAH but may not be an independent outcome factor *(13)*. Direct brain oxygen (BtO_2) monitoring is now common in neurocritical care. Several clinical studies demonstrate that cerebral hypoxia, cerebral ischemia, or infarction can occur despite normal ICP and cerebral perfusion pressure (CPP; *14–17*). In addition, reduced BtO_2 appears to be an independent risk factor for poor outcome in brain injury *(17–21)*. In this study, we therefore examined whether IAP alters BtO_2.

Materials and Methods

Patient Population and Methods

Patients were retrospectively identified from a prospective observational database that described patients who underwent BtO_2 monitoring. Patients included in this study had: (1) known SAH from a radiographically documented aneurysm; (2) admission clinical Hunt & Hess grade IV or V; (3) a BtO_2 monitor, and (4) IAP for cerebral vasospasm. Data in the observational database were abstracted from patient hospital records, including clinical notes, intensive care unit (ICU) flow sheets, operative reports, anesthetic records, review of head computed tomography (CT) scans, and angiograms. The diagnosis of vasospasm was confirmed by angiography and each patient's angiogram before and after IAP was reviewed.

Monitors and Physiologic Variables

ICP, brain temperature (BT), and BtO_2 were monitored continuously using commercially available products (Licox, Integra Neuroscience, Plainsboro, NJ). The intracranial monitors (ICP, BT, and BtO_2) were inserted through a burrhole into the frontal lobe. At admission, the monitors were placed in the brain area of expected vasospasm determined by the distribution of subarachnoid blood on CT scan and by aneurysm location. The monitors were placed in the right frontal region for aneurysms that involved the anterior communicating artery (AcoA). When the monitors were inserted in a delayed fashion, they were placed ipsilateral to the worst middle cerebral artery (MCA) blood flow velocity (BFV) identified on transcranial Doppler (TCD). Heart rate, blood pressure, through an arterial line, and arterial oxygen saturation (SaO_2), also were recorded in all patients. CPP was calculated from the measured parameters (CPP = MAP – ICP). All physiologic variables were continuously recorded using a bedside monitor (Component Monitoring System M1046-9090C, Hewlett Packard, Andover, MA) linked to a computerized multimodality data acquisition system (MP100, Biopac, Goleta, CA). Data points were recorded every 2 seconds.

Vasospasm Management Protocol

Patients received care in the Neurosurgery Intensive Care Unit (NICU) according to a standard policy consistent with published recommendations for SAH *(1,22,23)*. This included: (1) early aneurysm occlusion using microvascular techniques or Guglielmi detachable coils (GDC) based on aneurysm morphology; (2) intubation and mechanical ventilation when the Glasgow Coma Scale (GCS) score was less than or equal to 8 to maintain $PaCO_2$ between 30 and 40 mmHg; (3) a ventriculostomy for hydrocephalus; (4) phenytoin for 2 weeks unless there were seizures; and (5) nimodipine for 21 days. All patients received a baseline crystalloid infusion (0.9% normal saline, 20 mEq/L KCl infused at 100 to 125 mL/hour starting on admission until post-SAH day 14 to maintain euvolemia. Patients were transfused with packed red blood cells if their hemoglobin was less than 7 or when clinically indicated. Hypervolemia (central venous pressure ≥12 mmHg or pulmonary artery diastolic pressure [PADP] ≥14 mmHg when a Swan-Ganz catheter was inserted) was maintained using intravenous albumin 5% 250 cc every 2–4 hours, alternating with 250 mL 0.9% normal saline. Symptomatic vasospasm, diagnosed by neurological deterioration (a GCS deterioration ≥2 or a new focal neurologic deficit), CT scan, and elevated TCD BFVs (a rapid increase in TCD velocities, middle cerebral BFV > 200cm/second, or the Lindegaard ratio was >8) was treated with intravenous phenylephrine (0.3 μg/[kg • minute]) to augment blood pressure titrated to the level where the neurologic deficit resolved or to increase baseline mean arterial blood pressure 25–30% to a maximum systolic blood pressure of 200 mmHg. When the neurologic deficit did not resolve within 3 hours, dobutamine was added to augment cardiac output and patients were considered candidates for IVP or balloon angioplasty.

Intra-Arterial Papaverine

Severe arterial narrowing was confirmed by 4-vessel diagnostic cerebral angiogram performed in the standard fashion using nonionic, water-soluble contrast (Omnipaque-300, Nycomed, Oslo, Norway). Patients were considered for balloon angioplasty or IAP when severe arterial narrowing (>75% vessel lumen narrowing) was identified in a vessel distribution consistent with the neurologic examination. In general, balloon angioplasty was favored for internal carotid artery (ICA) or MCA spasm, whereas IAP was used for anterior cerebral artery (ACA) spasm or as an adjunct to allow balloon angioplasty. During the procedure, patients received general anesthesia using midazolam and fentanyl. For IAP, a 5- or 6-French catheter was positioned in the ICA ipsilateral to the narrowed vessel and 240 to 300 mg of papaverine chloride (in 100 mL normal saline) was infused over 5 to 50 minutes. The response to IAP was documented by repeat angiogram once IAP was complete.

Data and Statistical Analysis

Continuously monitored MAP, ICP, BtO_2, CPP, and SaO_2 were obtained for 10 minutes before, during, and for 10 minutes after IAP. All parameter values obtained during each time frame were averaged and then the data for all patients was grouped for statistical comparison. Data are expressed as the mean ± the standard deviation of the mean. When the data was not normally distributed, the median is used to describe the data. A paired, two-sample Student's *t*-test was used to test for significance. Linear relationships were examined using Spearman's correlations. Statistical significance was defined as a p value of less than 0.05. All statistical analysis was performed

using commercially available software, SAS version 8.2 (SAS institute Inc., Gary, NC) and Instat Version 2.03 (GraphPad Software, San Diego, CA).

Results

Vasospasm and Angiography

Data are available for five patients (median age 58). Papaverine infusion was performed between days 4 and 7. Symptomatic vasospasm was diagnosed because of a new focal neurological finding ($n = 3$) or a decline in consciousness ($n = 2$). Severe arterial narrowing was confirmed on angiography in each patient. The ICP, BT, and BtO_2 monitors were ipsilateral to the vessels that received IAP in all patients. There were no immediate complications following diagnostic cerebral angiography and IAP. All patients had at least partial reversal of vasospasm following SAH, as evidenced by angiography during the treatment.

Physiologic Variables and ICP

The FiO_2 was kept constant with an automated ventilator during IAP. In addition, SaO_2 was monitored continuously and remained stable in each procedure. Baseline MAP was 110.55 ± 1.36 mmHg and remained unchanged (Figure 1A) during IAP infusion (110.90 ± 2.00 mmHg; $p = 0.31$). Mean baseline ICP (defined as mean ICP in the 10 minutes immediately before IAP) was 23.04 ± 1.18 mmHg. ICP increased immediately (within 1 to 3 minutes) with IAP infusion in all patients and remained elevated during the procedure (Figure 1B). The mean ICP obtained by averaging values during IAP infusion was 29.89 ± 1.18 mmHg ($p < 0.05$). ICP trended towards baseline 10 minutes after IAP ended in all five patients and returned to baseline within 60 minutes of IAP in all patients.

Brain Oxygen

Baseline BtO_2 was 32.99 ± 1.45 mmHg. BtO_2 decreased in all five patients. This decrease was observed within 4 minutes of the start of IAP and on average was 37.5%. Mean BtO_2 during IAP (22.96 ± 2.9 mmHg; $p < 0.05$; Figure 1C) was significantly less than baseline (32.99 ± 1.45 mmHg). There was a modest relationship between the ICP increase (ΔICP) and BtO_2 decrease (ΔBtO_2) (Figure 2; $R^2 = 0.526$). BtO_2 returned to baseline within 10 minutes after IAP in all five patients. Figure 3 represents continuous data taken from one patient, which demonstrates the relationship between ICP and BtO_2. The dose of papaverine each patient received was similar so we could not establish a dose-response.

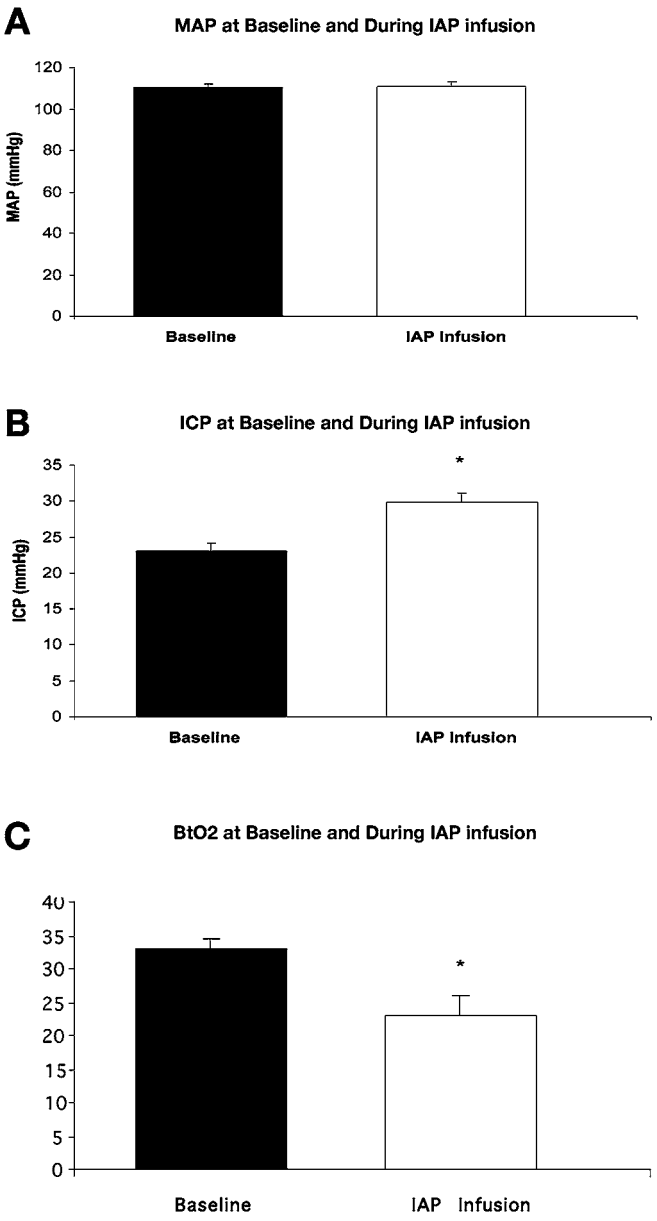

Fig. 1. Histograms displaying **(A)** mean (±SD) mean arterial pressure (MAP), **(B)** mean intracranial pressure (ICP), and **(C)** brain tissue oxygen (BtO_2) at baseline and during infusion of intra-arterial papaverine (IAP). Statistical significance ($p < 0.05$) is denoted by *.

Discussion

In this study, we present physiologic data from five patients who received IAP for symptomatic cerebral vasospasm. MAP was stable during IAP. However, an immediate and sustained ICP increase was observed within minutes of starting IAP. The ICP remained elevated during the entire infusion period and only began to return towards baseline 5 to 10 minutes after the end of IAP. In all cases BtO_2 decreased significantly during IAP and returned toward baseline once IAP was ended. These results may help explain why papaverine, although successful in reversing the arterial narrowing of vasospasm, has not resulted in improved patient outcome *(5,9)*.

Methodological Limitations

There are several potential limitations to our study. First, the sample size is small and there is no control group because this was an observational study only. This suggests our results should be considered as preliminary. However, the data are compelling in that BtO_2 reduced in all patients during IAP and are consistent with previous reports that show ICP can

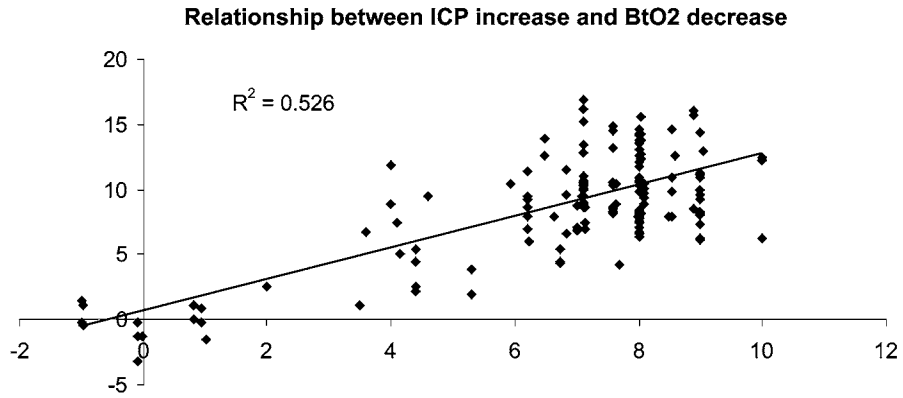

Fig. 2. Scattegram displaying the change in brain tissue oxygen (ΔBtO_2) as a function of increase in intracranial pressure (ΔICP). Individual data points are obtained by calculating the difference between each time point and the baseline value (averaged over 10 minutes) for each patient. The correlation coefficient (R^2) is 0.526.

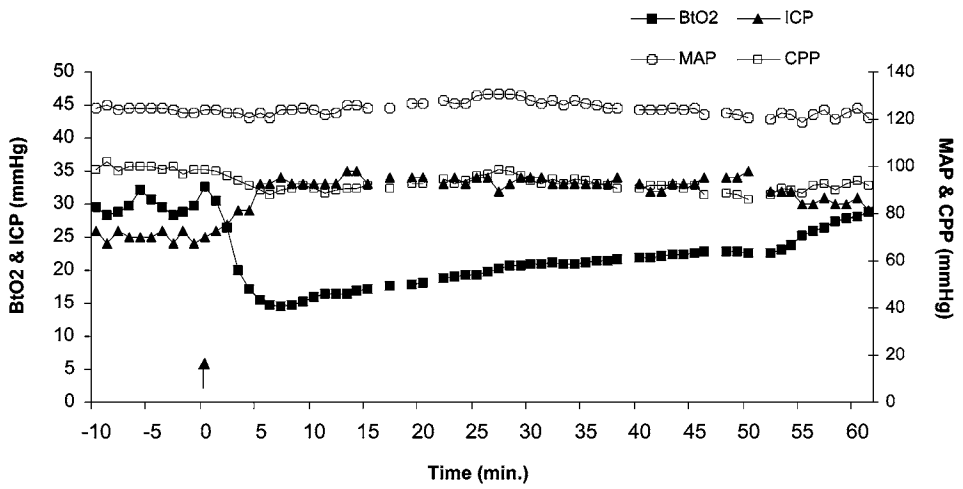

Fig. 3. Line graphs illustrating continuous mean arterial pressure (MAP), intracranial pressure (ICP), cerebral perfusion pressure (CPP), and brain tissue oxygen (BtO_2) monitoring performed in a single patient before, during, and following the intra-arterial infusion of papaverine (IAP). The physiologic variables are plotted at minute intervals. The start of IAP is defined as time = 0 minutes (designated by vertical arrow), and continued for 50 minutes. Papaverine infusion is associated with an increase in ICP and a decrease in BtO_2 while the MAP remains stable. BtO_2 and ICP return to baseline at t = 60 minutes.

increase during IAP (24). Second, the BtO_2 monitor we used records local BtO_2 within white matter. In each case the monitor was on the same side as the maximal arterial narrowing and IAP. However, the probe may not be in the distribution of the vessel that receives IAP. Although this may influence the BtO_2 reading, we do not think it will alter the conclusion of this report because when the BtO_2 monitor is in "undamaged" brain areas the values can be extrapolated to examine global oxygenation (25). In addition, each patient underwent a head CT scan before IAP so we were able to confirm that the probe was in "normal" white matter (i.e., free of infarct or contusion). Third, outlier values or minute-to-minute BtO_2 variability may influence the results. We think this unlikely because all values obtained from continuous recording during the 10 minutes before IAP and in subsequent time blocks during and after IAP were averaged and the mean or median used in analysis. In our experience the normal minute-to-minute variability and even hour-to-hour BtO_2 variability, in the absence of physiologic or pathologic influences is less than 1–2 mmHg. This variability is less than the observed BtO_2 change after IAP when all patients are considered. Consequently, we believe the results accurately depict the general tendencies of change in all recorded variables.

Papaverine for Vasospasm

Vasospasm, the arterial narrowing observed after aneurysmal SAH is a major cause of preventable morbidity and mortality. Despite much research an effective therapy remains elusive (1,26). For those patients whose vasospasm is refractory to medical measures, endovascular strategies such as balloon angioplasty or IAP are advocated (2). Angiographic resolution of vasospasm after selective arterial dilation using angioplasty or IAP is described in several clinical reports

(3–7,9,10,27). The effects of balloon angioplasty are generally long lasting, whereas IAP appears to be more transient and so repeat IAP may be necessary in the same patient *(2,3)*. IAP can be used to treat smaller distal branches and diffuse spasm unlike balloon angioplasty, which is used in more proximal arteries. In addition, IAP can be used with balloon angioplasty to facilitate entry into spastic vessels or to treat ACA spasm where microcatheter navigation may occasionally be limited *(9)*. Several clinical reports *(4,6,7,10)* suggest that IAP is an effective stand-alone therapy for cerebral vasospasm because it can reverse or improve arterial narrowing. However, in other clinical studies IAP does not appear to benefit patient outcome *(5,9)*. The reasons for this are unclear. Nevertheless, IAP remains an important tool in vasospasm management.

Physiological Effects of IAP

Papaverine is a benzylisoquinoline opium alkaloid that dilates spastic vessels independently of endothelium-derived factors. It results in smooth muscle relaxation through phosphodiesterase inhibition and so causes nonspecific arteriolar vasodilatation. However, the extent and duration of the vasodilatory action of papaverine is unpredictable and repeat administration often is required to sustain vasodilatation *(3)*. Systemic hypotension can occur when papaverine is administered. However, this problem is avoided by supraselective intra-arterial infusion. There has been limited study of the physiologic effects of IAP and in particular its effects on BtO_2. Cross et al. *(11)* and McAuliffe et al. *(24)* have reported that ICP can increase following IAP, whereas Fandino et al. *(28)* demonstrated that IAP can improve reduced cerebral oxygenation in the short term when assessed by using cerebral arteriovenous oxygen and lactate differences. There are limitations to jugular catheters and up to 50% of jugular catheter readings may be inaccurate *(29)*. Thermal diffusion flowmetry studies also suggest that IAP may improve cerebral metabolism *(30)*. This technique however is an indirect measure of BtO_2.

In this report, we used direct BtO_2 monitoring. Our results demonstrate that a significant decrease in BtO_2 occurs during IAP. This decrease may in part be related to an associated increase in ICP. However not all reductions in BtO_2 are related to altered ICP *(15)* or perfusion pressure *(31)*. This may be important because thermal diffusion studies suggest cerebral blood flow (CBF) is transiently increased during IAP *(32)*. Increased CBF, however, does not mean cellular oxygen is improved. Recently Smith et al. *(12)* found that papaverine preserved with chlorobutanol was associated with neurological decline. This neurotoxicity was limited to the vascular territories of the areas exposed to papaverine. It remains unclear if this toxicity is a direct effect of papaverine or chlorobutanol, or if it is associated with ischemia induced by either chemical. Because this was an observational study, we do not have a blinded control group to determine what happens to BtO_2 when the carotid artery is infused with saline or the vehicle in which papaverine is dissolved. However, we have recorded ICP and BtO_2 during diagnostic angiography; no changes in either variable are observed. In addition, there is no adverse effect on BtO_2 during balloon angioplasty, suggesting that the BtO_2 reduction during IAP most likely is associated with papaverine or its vehicle.

The Importance of Reduced BtO_2

Several studies suggest that BtO_2 monitors are safe, sensitive, and can complement ICP monitors. In particular, cerebral hypoxia, defined as BtO_2 less than 15 mmHg is associated with poor outcome after traumatic brain injury (TBI), particularly when the episode is greater than 30 *(17–21)*. There has been limited study of BtO_2 in SAH *(33–35)*. In the acute phase following experimental SAH, BtO_2 is reduced *(33)*. The importance of this is uncertain because in clinical studies a relationship between cerebral hypoxia and outcome may occur late rather than early in monitoring *(34)*. On the other hand we have observed among 46 poor-grade patients with SAH who have had BtO_2 monitors that therapy to increase BtO_2 during episodes of cerebral hypoxia was significantly more successful in survivors than in nonsurvivors (Ramakrishna et al., unpublished observations).

An IAP-induced reduction in BtO_2 may be considered a secondary cerebral insult. Secondary cerebral insults can adversely affect outcome after SAH *(36)*. In part this explain why IAP does not necessarily improve patient outcome despite its reversal of arterial narrowing. Whether the decrease in BtO_2 needs to reach hypoxic levels to aggravate outcome is unclear and is not addressed by this study. However, we believe that any reduction in BtO_2 may be significant. For example, Meixensbeger et al. *(37)* observed no benefit to patient outcome by increasing CPP when BtO_2 was less than 10 mmHg (i.e., already severely hypoxic). By contrast, we have observed that therapy to keep BtO_2 greater than 20 mmHg is associated with improved outcome in TBI *(38)* and that reversal of cerebral hypoxia in SAH also is associated with better outcome (Ramakrishna et al., unpublished observations). The findings in the present report suggest that alternate strategies such as intra-arterial nicardipine or verapamil should be considered for vasospasm *(39)*, although the effects of these substances on cerebral metabolism are not well defined. However, more importantly, they raise the question as to how we define the end point of successful endovascular treatment of vasospasm and a subsequent impact on clinical outcome—reversal of arterial narrowing or a favorable effect on brain metabolism. Further study will be needed to answer this important question, particularly as new treatment modalities such as intrathecal delivery of nitric oxide donors or the systemic administration of endothelin antagonists become available.

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