effective at preventing and reversing angiographic vasospasm to a certain extent, but this reversal or prevention of angiographic vasospasm does not translate into as marked an improvement in outcome as would be anticipated by the reduction in angiographic vasospasm. Without being limited by theory, it is postulated that the systemic delivery of the voltage-gated calcium channel antagonists may cause side effects that mitigate the beneficial effects on angiographic vasospasm, such as, for example, systemic hypotension and pulmonary vasodilation with pulmonary edema, which prevent the administration of higher systemic doses. Dilation of blood vessels in the lungs also may cause lung edema and lung injury. Second, and without being limited by theory, it is postulated that systemic deliveyr of the voltage-gated calcium channel antagonists may limit other effects of SAH that contribute to DCI, including cortical spreading ischemia and microthromboemboli.

[000149] While conventional therapies have been focusing on treating cerebral vasospasms following subarachnoid hemorrhage, accumulating evidence suggests that there are additional complications derived from subarachnoid hemorrhage, which need to be targeted for treatment interventions in order to improve prognosis following subarachnoid hemorrhage treatment. The described invention offers such an approach.

SUMMARY

[000150] According to one embodiment~~aspect~~, the disclosure~~described invention~~ provides a method of treating at least one cerebral artery in a subarachnoid space at risk of interruption due to a brain injury in a human subject, comprising: a) providing a flowable sustained release microparticulate composition comprising (i) a microparticulate formulation comprising a therapeutic amount of at least one therapeutic agent, wherein the microparticulate formulation comprises a plurality of microparticles of uniform size distribution, wherein the therapeutic agent is dispersed throughout each microparticle, and wherein the therapeutic amount is effective to treat a delayed complication of the interruption of the cerebral artery, (ii) and a pharmaceutical carrier; and b) administering the composition locally into a cerebral ventricle so that the microparticulate formulation flows from the cerebrospinal fluid (CSF) in the cerebral ventricle into the cerebrospinal fluid (CSF) in the subarachnoid space before releasing the therapeutic agent in the subarachnoid space, wherein the therapeutic agent contacts and flows around the at least one cerebral artery in the subarachnoid space without

mm from the cerebral artery in the subarachnoid space. According to another embodiment, the cerebral ventricle is a lateral ventricle, a third ventricle, a fourth ventricle, or a combination thereof. According to another embodiment, the flowable sustained release microparticulate composition produces a predominantly localized effect around the cerebral artery in the subarachnoid space. According to another embodiment, the therapeutic amount of the therapeutic agent is effective to increase the internal diameter of the cerebral artery in the subarachnoid space. According to another embodiment, the pharmaceutical carrier is a buffer solution.

[000150a] According to one aspect, there is provided the use of a microparticulate composition comprising (a) a microparticulate formulation comprising a therapeutic amount of at least one therapeutic agent, wherein the therapeutic amount is effective to treat a delayed complication of the interruption of the cerebral artery, the microparticulate formulation being characterized by: (i) a plurality of microparticulates of uniform size distribution; (ii) dispersal of the therapeutic amount of the therapeutic agent throughout each microparticle, in a core surrounded by a coating; adsorbed into the particles or a combination thereof; (iii) sustained release of the therapeutic amount of the therapeutic agent from each microparticle; (iv) as a dispersion, its flowability around a cerebral artery in a subarachnoid space of the brain at risk of interruption due to a brain injury, (b) and a pharmaceutical carrier; in the manufacture of a medicament for treating at least one cerebral artery in a subarachnoid space at risk of interruption due to a brain injury in a human subject, and wherein the composition is to be administered locally into a cerebral ventricle such that the therapeutic agent contacts and flows around the at least one cerebral artery in the subarachnoid space without entering systemic circulation in an amount to cause unwanted side effects.

[000151] According to another aspect, there is provided a microparticulate composition comprising: (i) a microparticulate formulation comprising at least one therapeutic agent, and (ii) a pharmaceutically acceptable carrier, wherein the microparticulate composition is formulated for delivery into a cerebral ventrical; the microparticulate formulation being characterized by: (iii) a plurality of microparticle of uniform size distribution, (iv) dispersal of the therapeutic amount of the therapeutic agent throughout each microparticle, in a core surrounded by a coating; adsorbed

into the particles or a combination therof; (v) sustained release of the therapeutic amount of the therapeutic agent from each microparticle; (vi) as a dispersion, its flowability around a cerebral artery in a subarachnoid space of the brain at risk of interruption due to a brain injury. According to another embodimentaspect, the disclosuredescribed invention provides a flowable sustained release microparticulate composition comprising: (i) a microparticulate formulation comprising at least one therapeutic agent, and (ii) a pharmaceutically acceptable carrier, wherein the microparticulate formulation comprises a plurality of microparticles of uniform size distribution, wherein the at least one therapeutic agent is dispersed throughout each microparticle, and wherein the composition is suitable for delivery into a cerebral ventricle and is capable of flow in the cerebrospinal fluid (CSF) from the ventricle into the subarachnoid space. According to one embodiment, the therapeutic agent is a calcium channel antagonist, an endothelin antagonist, a transient receptor potential (TRP) protein antagonist, or a combination thereof. According to another embodiment, the microparticles comprise a matrix. According to another embodiment, the flowable sustained release microparticulate composition, upon delivery into the cerebral ventricle, is capable of flow from the cerebrospinal fluid (CSF) in the cerebral ventricle into the cerebrospinal fluid (CSF) in the subarachnoid space before sustained release of the therapeutic agent in the subarachnoid space. According to another embodiment, the therapeutic agent is a calcium channel antagonist selected from the group consisting of an L-type voltage dependent calcium channel inhibitor, an R-type voltage dependent calcium channel inhibitor, an N-type voltage dependent calcium channel inhibitor, a P/Q-type voltage dependent calcium channel inhibitor, a T-type voltage dependent calcium channel inhibitor, or a combination thereof. According to another embodiment, the L-type voltage dependent calcium channel inhibitor is a dihydropyridine, selected from the group consisting of amlodipine, aranidipine, azelnidipine, bamidipine, benidipine, cinaldipine, efonidipine, felodipine, isradipine, lacidipine, lemildipine, lercanidipine, nicardipine, nifedipine, nilvadipine, nimodipine,

nisoldipine, nitrendipine, manidipine, pranidipine, or a combination thereof. According to another embodiment, the dihydropyridine is nimodipine. According to another embodiment, the microparticulate formulation comprises a powder suspension of microparticles. According to another embodiment, the microparticulate formulation further comprises a slow-release compound. According to one embodiment, the slow release compound is a biodegradable polymer. According to one embodiment, the biodegradable polymer is selected from the group consisting of polylactide-polyglycolide, poly(orthoester), and poly(anhydride). According to another embodiment, the sustained release of the therapeutic amount of the therapeutic agent is capable of occurring within a half-life ranging from 1 day to 30 days from delivery of the composition to the cerebral ventricle. According to another embodiment, the cerebral ventricle is at least 0.001 mm from the cerebral artery in the subarachnoid space. According to another embodiment, the cerebral ventricle is a lateral ventricle, a third ventricle, a fourth ventricle, or a combination thereof. According to another embodiment, the flowable sustained release microparticulate composition is capable of producing a predominantly localized effect around the cerebral artery in the subarachnoid space. According to another embodiment, the therapeutic amount of the therapeutic agent is effective to increase the internal diameter of the cerebral artery in the subarachnoid space. According to another embodiment, the pharmaceutical carrier is a buffer solution.

[000152] According to another aspect, there is provided a sterile kit for treating at least one cerebral artery in a subarachnoid space at risk of interruption due to a brain injury comprising: (i) a sterile injection apparatus; (ii) a sterile first syringe comprising a barrel, and a plunger; (iii) a sterile second syringe comprising a barrel and a plunger; (iv) a sterile female luer cap; (v) a sterile male luer cap; (vi) a sterile female syringe connector; (vii) a sterile microparticulate formulation for administration into a cerebral ventricle comprising a therapeutic amount of at least one therapeutic agent, wherein the therapeutic amount is effective to reduce a delayed complication of an interruption of a cerebral artery in a subarachnoid space, the microparticulate formulation being characterized by: (i) a plurality of microparticles of uniform size distribution, (ii) dispersal of the therapeutic amount of the therapeutic agent throughout each

microparticle, in a core surrounded by a coating; adsorbed into the particles or a combination thereof; (iii) sustained release of the therapeutic amount of the therapeutic agent from each microparticle; (iv) as a dispersion, its flowability around a cerebral artery in a subarachnoid space of the brain at risk of interruption due to a brain injury, and (viii) a sterile pharmaceutically acceptable carrier. According to another embodimentaspect, the disclosuredescribed invention provides a sterile kit for treating at least one cerebral artery in a subarachnoid space at risk of interruption due to a brain injury comprising: (i) a sterile surgical injection apparatus; (ii) a sterile first syringe comprising a barrel, and a plunger; (iii) a sterile second syringe comprising a barrel and a plunger; (iv) a sterile female luer cap; (v) a sterile male luer cap; (vi) a sterile female syringe connector; (vii) a sterile microparticulate formulation suitable for administration into a cerebral ventricle comprising a therapeutic amount of at least one therapeutic agent, wherein the therapeutic amount is effective to reduce a delayed complication of an interruption of a cerebral artery in a subarachnoid space, wherein the microparticulate formulation comprises a plurality of microparticles of uniform size distribution, and wherein the at least one therapeutic agent is dispersed throughout each microparticle, and (vii) a sterile pharmaceutically acceptable carrier. According to one embodiment, the surgical injection apparatus is a needle, a cannula, a catheter, or a combination thereof. According to another

embodiment, the microparticulate formulation comprises a powder suspension of microparticles. According to another embodiment, the microparticles have a diameter ranging from about 30 μm to about 100 μm. According to another embodiment, the microparticulate formulation further comprises a slow-release compound. According to one embodiment, the slow release compound is a biodegradable polymer. According to another embodiment, the biodegradable polymer is selected from the group consisting of polylactide-polyglycolide, poly(orthoester), and poly(anhydride). According to another embodiment, the at least one therapeutic agent is a calcium channel antagonist, an endothelin antagonist, a transient receptor potential (TRP) protein antagonist, or a combination thereof. According to another embodiment, the calcium channel antagonist is selected from the group consisting of an L-type voltage dependent calcium channel inhibitor, an R-type voltage dependent calcium channel inhibitor, an N-type voltage dependent calcium channel inhibitor, a P/Q-type voltage dependent calcium channel inhibitor, a T-type voltage dependent calcium channel inhibitor, or a combination thereof. According to another embodiment, the L-type voltage dependent calcium channel inhibitor is a dihydropyridine, selected from the group consisting of amlodipine, aranidipine, azelnidipine, bamidipine, benidipine, cinaldipine, efonidipine, felodipine, isradipine, lacidipine, lemildipine, lercanidipine, nicardipine, nifedipine, nilvadipine, nimodipine, nisoldipine, nitrendipine, manidipine, pranidipine, or a combination thereof. According to another embodiment, the dihydropyridine is nimodipine. According to another embodiment, the pharmaceutical carrier is a buffer solution. According to another embodiment, the kit further comprises at least two sterile containers, wherein the sterile first container is suitable to hold the sterile microparticulate formulation and the sterile second container is suitable to hold the sterile pharmaceutical carrier. According to another embodiment, the container is a vial, a bottle, a tube, a bag, a packet, a pillow, an ampoule, or a combination thereof. According to another embodiment, the microparticulate formulation is prepacked in the first syringe. According to another embodiment, the pharmaceutical carrier is prepacked in the second syringe.

[000153] According to another aspect, there is provided a method of preparing a sterile flowable sustained release microparticulate composition comprising, in order: (a) providing a sterile microparticulate formulation comprising a therapeutic amount of at least one therapeutic agent, wherein the therapeutic amount is effective to reduce a delayed complication of an interruption of a cerebral artery in a subarachnoid space, the microparticle formulation being characterized by: (i) a plurality of microparticles of uniform size distribution. (ii) dispersal of the therapeutic amount of the therapeutic agent throughout each microparticle, in a core surrounded by a coating; adsorbed in the particles or a combination thereof; (b) drawing the sterile microparticulate formulation of step (a) into a sterile first syringe comprising a first syringe barrel, a first syringe plunger and a female luer cap, and removing air trapped within the first syringe; (c) providing a sterile pharmaceutically acceptable carrier; (d) drawing the sterile pharmaceutical carrier of (c) into a sterile second syringe fitted with a male luer cap comprising a second syringe barrel and a second syringe plunger; (e) replacing the male luer cap in step (c) with a sterile female syringe connector; (f) connecting the sterile first syringe containing the sterile microparticulate formulation of step (b) with the sterile second syringe containing the sterile pharmaceutically acceptable carrier of step (c) via the female syringe connector of step (d); (g) pushing the sterile first syringe plunger so that the sterile microparticulate formulation and the sterile pharmaceutical carrier mix in the sterile second syringe barrel; (h) pushing the sterile second syringe plunger so that the sterile microparticulate formulation and the sterile pharmaceutical carrier mix in the sterile first syringe barrel; and (i) repeating steps (g) and (i) at least 5-50 times to yield the sterile flowable sustained release microparticulate composition for delivery into a cerebral ventricle. According to another embodiment~~aspect~~, the described disclosure~~invention~~ provides a method of preparing a sterile flowable sustained release microparticulate composition comprising: (a) providing a sterile microparticulate formulation comprising a therapeutic amount of at least one therapeutic agent, wherein the therapeutic amount is effective to reduce a delayed