NicaPlant

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see also Nicardipine for aneurysmal subarachnoid hemorrhage.

To obtain sufficient nicardipine drug concentration at the site of action without observing the systemic side effects the drug needs to be delivered in close proximity to the place where it should be active.

This can be obtained by placing it in close contact with the wall of the cerebral artery at the time of aneurysm clipping, in this way circumventing the blood-brain barrier. The selection of the calcium channel blocker nicardipine, contained in NicaPlant® is based on its chemical-physical characteristics and a prospective randomized multicenter Phase 2b trial, Vajkoczy et al. could demonstrate the safety and efficacy of NicaPlant® implants in preventing CV in patients with SAH [1)].

Orphan designation

Developer

https://www.bit-pharma.com/product/

Trials

The trial was performed as an international randomized, controlled study, single-blinded study multicenter study. 40 Patients with World Federation of Neurosurgical Societies grading for subarachnoid hemorrhage 3 and 4 undergoing surgical repair of their ruptured aneurysm were randomized to receive ten pellets of NicaPlant® (40 mg) plus standard of care or standard of care alone. The implants were administered immediately following clip ligation of the ruptured aneurysm in proximity to all the exposed cerebral blood vessels. The primary endpoint was the incidence of moderate to severe cerebral vasospasm (day 8 ± 1). A blinded independent outcome accessor analyzed all imaging data.

In the implant group, 20% (4/20) of patients reached the primary endpoint, compared to 58% (11/19) of patients in the control group ($p = 0.024$). Including mild CV, 75% of all patients in the control group developed CV compared to 30% in the implant group ($p = 0.0129$). 32% (6/19) of the patients in the control group developed new cerebral infarction, compared to 10% (2/20) in the implant group ($p = 0.1273$). Endovascular rescue therapy was performed in 10% of the patients in the implant group compared to 58% in the control group ($p = 0.002$). 4 subjects (20%) in the control group experienced Treatment-emergent adverse events (TEAE), compared with none in the active group [2)].

https://clinicaltrials.gov/ct2/show/NCT04269408

Animal Studies

Bayerl et al. tested in vitro the release dynamics of a novel formulation of the calcium channel blocker nicardipine and in vivo local tolerance and tissue reaction using a chronic cranial window model in mice. To characterize the release kinetics in vitro, dissolution experiments were performed using artificial cerebrospinal fluid over a time period of 21 days. The excipients used in this formulation (NicaPlant) for sustained nicardipine release are a mixture of two completely degradable polymers. A chronic cranial window in C57BL/6 mice was prepared, and NicaPlant slices were placed in proximity to the exposed cerebral vasculature. Epifluorescence video microscopy was performed right after implantation and on days 3 and 7 after surgery. The vessel diameter of the arteries and veins, vessel permeability, vessel configuration, and leukocyte-endothelial cell interaction were quantified by computer-assisted analysis. Immunofluorescence staining was performed to analyze inflammatory reactions and neuronal alterations.

In vitro, the nicardipine release profile showed an almost linear curve with about 80% release on day 15 and full release on day 21. In vivo, epifluorescence video microscopy showed a significantly higher arterial vessel diameter in the NicaPlant group due to vessel dilatation (21.6 ± 2.6 µm vs 17.8 ± 1.5 µm in controls, $p < 0.01$) confirming vasoactivity of the implant, whereas the venous diameter was not affected. Vessel dilatation did not have any influence on the vessel permeability measured by contrast extravasation of the fluorescent dye in epifluorescence microscopy. Further, an increased leukocyte-endothelial cell interaction due to the implant could not be detected. Histological analysis did not show any microglial activation or accumulation. No structural neuronal changes were observed [3].

[1], [2]
Vajkoczy, Peter MD; Thomé, Claudius; Kerschbaumer, Johannes; Meyer, Bernhard MD; Wostrack, Maria; Adage, Tiziana; Breitenbach, Jörg; Bavinzski, Gerhard; Hirschmann, Dorian; Bendszus, Martin; Rohde, Veit; Mielke, Dorothee; Wessels, Lars. 104 A Safety and Efficacy Study of NicaPlant® in Aneurysmal Subarachnoid Haemorrhage Patients Undergoing Aneurysm Clipping. Neurosurgery 69(Supplement_1):p 23, April 2023. | DOI: 10.1227/neu.0000000000002375_104

[3]
Bayerl SH, Ghori A, Nieminen-Kelhä M, Adage T, Breitenbach J, Vajkoczy P, Prinz V. In vitro and in vivo testing of a novel local nicardipine delivery system to the brain: a preclinical study. J Neurosurg. 2019 Jan 25;132(2):465-472. doi: 10.3171/2018.9.JNS173085. PMID: 30684943.