Complete Inclusion Criteria

1. The patient was of age 18 to 65 years.
2. The patient was in a coma with severe TBI and a GCS 3–7 including a maximum score of 1 on the eye-opening scale and on the best verbal response scale, and a score of 1 to 5 on the motor scale as initially assessed (e.g., by the emergency physician) after resuscitation and haemodynamic stabilisation but before intubation and/or sedation. (Note: the study physician was to use his own judgment, on the basis of the report of the emergency doctor and the current status of the patient, that the coma was due to trauma. Patients who had a GCS above 8 and/or were not comatose and/or were not comatose at the scene where the trauma occurred but whose condition deteriorated [e.g., during transport to the hospital] could still be eligible for the study. The lowest (worst) possible GCS is 3, the highest 15.)
3. The patient had a blunt severe head trauma.
4. The patient was haemodynamically stable (systolic blood pressure > 90 mmHg) after resuscitation/stabilisation.
5. The start of treatment with study medication was feasible within 4.5 hours of onset of TBI. (Note: onset of TBI was the time of impact—i.e., if an interval was provided for time of impact—e.g., between 10:00 and 11:00 hours—the earlier end of that interval, 10:00 hours, was to be assumed as the time of impact.)
6. Informed consent was obtained according to national and local legislation.
7. For all female patients: a urine pregnancy test gave a negative result.

Complete Exclusion Criteria

1. The TBI was due to penetrating head injuries or gunshot wounds.
2. Any major spinal cord injury was present.
3. The patient had initially bilateral non-reactive dilated pupils.
4. The patient had sustained major injury that required or was expected to require > 2500 mL of blood (> 5 blood units) within the 12 hours following TBI. (Note: patients requiring decompressive surgery could still be eligible for this study.)
5. There was known—or CT (computed tomography) scan evidence of—previous major cerebral damage.
6. The coma was due to causes other than TBI.
7. The patient had received an experimental drug within the 4 weeks before the current injury.
8. The patient had a known history of disability that might interfere with subsequent evaluation.
9. Any severe concomitant disorder was present that might relevantly affect the safety of the patient, the efficacy of the drug (e.g., psychiatric disorders such as but not limited to dementia, schizophrenia, mania, personality disorders), or the metabolism of the drug (e.g., severe renal or hepatic disease).
10. The patient had any known hypersensitivity to any cannabinoid.
11. The patient was unlikely to be available for follow-up (e.g., patients from abroad).
12. The patient was unlikely to survive, as determined by qualified study physicians before randomisation.
13. The patients had any known CB intake in the three days before the TBI.

MRT Protocol

General: any tilt of the head was to be corrected with the help of the three scouts.

1. Scout view, three orientations.
2. Sagittal T2, 3 mm, minimum slice gap, direction of brainstem, parallel to midline.
3. Axial T2, T1, T2* of complete brain, 5 mm, minimum slice gap, parallel to AC–PC line. (Important: slices were to be acquired at identical positions and orientations, to make signal behaviour of the lesions in different sequences directly comparable.)
4. Special high-resolution imaging of brain stem.
5. Coronal T2, 3 mm, minimum slice gap, covering at least complete brain stem and 4th ventricle, parallel to bottom of 4th ventricle (so-called “line of Meynert”).
6. Axial T2, 3 mm, minimum slice gap, covering infratentorial space, orthogonal to 5.
7. Axial DWI of complete brain, 5 mm, minimal slice gap, parallel to AC–PC line. (Important: DWI images were to be acquired with at least three different b values (e.g., 0,500 and 1,000) to make calculation of numeric values such as ADC possible. The raw images were to be provided, because numerical analysis of DWI data was to be performed centrally.)
8. Optional: coronal FLAIR of complete brain, 5 mm, orthogonal to axial slices.

With respect to the inclusion criteria and the Firsching classification, brain stem was the main focus of MR imaging. Measurement nos. 1–6 were therefore mandatory, while measurement nos. 7–9 were optional. If any of the measurements described above could not be realised in total, then at least the infratentorial space was to be scanned with minimum slice gap and the best possible image quality.

CONSORT Diagram

Screened (n = 439)

Excluded because of non-fulfillment of inclusion criteria (n = 342):
- Age < 18 or > 65 years (n = 102)
- Trauma-to-treatment time > 4.5 hours (n = 106)
- Severity of TBI (n = 59)
- Other reason (n = 172)

Randomised and treated (n = 97)

High dose (n = 31)
- Study not completed (n = 6):
  - Consent withdrawn (n = 0)
  - Death (n = 4)
  - Loss to follow-up (n = 2)
- Study completed (n = 25)

Low dose (n = 33)
- Study not completed (n = 5):
  - Consent withdrawn (n = 1)
  - Death (n = 3)
  - Loss to follow-up (n = 1)
- Study completed (n = 28)

Placebo (n = 33)
- Study not completed (n = 9):
  - Consent withdrawn (n = 2)
  - Death (n = 5)
  - Loss to follow-up (n = 2)
- Study completed (n = 24)