

# Transcranial Route of Brain Targeted Delivery of Methadone in Oil

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The unique anatomical arrangement of blood vessels and sinuses in the human skull and the brain, the prevalence of a high density of skin appendages in the scalp, extracranial vessels of the scalp communicating with the brain via emissary veins and most importantly, the way that the scalp is used in *Ayurvedic* medical system in treating diseases associated with the brain show that a drug could be transcranially delivered targeted to the brain through the scalp. The present study was to investigate by measuring the antinociceptive effect on rats whether the opioid analgesic methadone could be delivered targeted to the brain by transcranial delivery route. A non aqueous solution of methadone base in sesame oil was used for the application on the scalp. Animal studies were carried out using six groups of male rats consisting of group 1, the oral control treated with distilled water 1 ml; group 2, the oral positive control treated with methadone hydrochloride solution 316.5 µg/ml; group 3, the negative control treated transcranially with the blank sesame oil 0.2 ml and three test groups 4, 5 and 6 treated with three different dose levels of the transcranial oil formulation of methadone base, 41.6 µg/0.2 ml, 104 µg/0.2 ml and 208 µg/0.2 ml, respectively. The antinociceptive effects were examined by subjecting the rats to the hot plate and tail flick tests. The two higher concentrations of the three transcranial methadone formulations yielded response vs time curves showing nearly equal maximum antinociceptive effects similar to that of the oral positive control. Maximum analgesic effect after transcranial administration was observed between 1st and 2nd h and declined up to 6th hour. The results indicate that the transcranial brain targeted delivery of methadone base in the form of an oil based non aqueous solution results in statistically significant antinociceptive effects under experimental conditions. Therefore, it is possible to deliver central nervous system drugs through the proposed transcranial route when suitably formulated.

Key words: Transcranial route (TCR), emissary veins, intracranial sinuses, catchment area, methadone base, rubbing in

Apart from the established routes of drug administration practiced in modern medicine, *Ayurvedic* system of medicine uses a special route which involves oil therapies to the head. These therapies are used for centuries to treat diseases of the central nervous system<sup>[1]</sup>. The drug delivery route under taken in the present study is incidental to a special anatomical feature of the skull. The emissary veins draining blood from extracranial sites into the intracranial sinuses pierce a series of foramina present in the cranial bones. Scalp veins communicate with the sinuses of the brain via emissary veins. There are thirteen emissary veins connecting extracranial sites of the head with intracranial sinuses<sup>[2]</sup>. Seven major sinuses within the skull are inter connected by

a number of anastomosing veins, which finally drain intracranially into jugular veins giving ample scope for the diffusion of the drug molecules into the nerve tissue of the brain. These anatomical arrangements of the vascular system of the brain are made use of in the investigations to establish the brain targeted transcranial route (TCR) of drug delivery.

TCR describes the passage of an oil solubilized drug moiety across the skin of the scalp including appendages of the skin such as sebaceous glands, walls of the hair follicles and sweat glands, through the cranial bones along with the diploe, the cranial bone sutures, the meninges and specifically through the emissary veins into the brain. It has to be noted that the total surface area of the skin along with the skin appendages adds up to a much larger area against the immediately visible plain skin surface in

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