Reconsidering the Use of Propranolol in the Treatment of Cosmetic Infantile Hemangiomas

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Up to 10% of infants (particularly females) are stricken with benign vascular tumors commonly referred to as strawberry marks and clinically defined as Infantile Hemangiomas (IHs). IHs are composed of aberrant microvascular endothelial cells that rapidly proliferate during the first 2 years of life, stabilize, and slowly involute until their disappearance somewhere within a few years after the child’s fifth birthday. These tumors can remain very small and unnoticeable (<1mm) or grow to overwhelming proportions (>20cm), and while the majority of IHs are harmless and are best left to naturally involute, approximately 10% of pediatric patients with IHs are faced with disfiguring and/or life threatening tumors based on their size or location. Patients with overly aggressive IHs require aggressive clinical intervention that typically involves surgery or systemic corticosteroid and/or beta blocker administration.

Historically anti-inflammatory corticosteroids have been considered the first line treatments against IHs with an efficacy rate at approximately 70%; however this treatment is also associated with double the rate of adverse side effects including altered growth, moon facies, osteoporosis, fungal infections, and hypertension. More recently, the beta blocker propranolol has been utilized as the gold standard of treatment against IHs, with an efficacy rate of close to 95%. The immediate side effects of beta blockade in these pediatric patients were largely limited to manageable changes in blood pressure, bradycardia, diarrhea, fatigue, and difficulty regulating body temperature. More and more vascular anomaly centers are using propranolol with great success and generally good control over acute side effects, however little discussion has been put forth regarding the long term side effects of systemic beta blockade in developing children. This concern becomes particularly important when clinicians are faced with the decision to use propranolol for cosmetic IHs that are small and non life threatening.

Noradrenaline neurotransmission becomes functional early in the development of the brain, and substantial data from a number of labs indicates that disrupting this signaling with beta receptor agonists may alter brain development. Indeed, evidence from human studies indicate that memory associated with emotional arousal results from activation of beta-adrenergic stress hormone systems during and after the emotional response. For instance, stimulation of beta adrenergic receptors located on the basolateral amygdala occurs during emotionally arousing events and modulates memory consolidation processes, allowing the brain to remember memories in proportion to the importance of the memory [1]. Likewise, propranolol has been shown to significantly impair retention of emotionally arousing memories while not affecting neutral memories [2-4]. It has been known for almost three decades that the right hemisphere of the brain controls more global, holistic aspects of a stimulus, while the left hemisphere is biased toward the finer details [5]. Moreover, hemispheric specialization is gender based, where the right amygdala in males and the left amygdala in females controls enhanced memory for emotional events [6,7]. In a study performed by Cahill and van Stegeren [8], the authors demonstrated that beta blockade markedly impaired sex related differences in memory retention of information central versus peripheral to the story following emotionally arousing information. These studies were performed on adult humans receiving acute beta blockade with a mean age of greater than 20 years old (i.e., their neurological pathways were largely developed at the time of beta blockade), yet it raises the question “What could beta blockade do to the susceptible developing brain of a neonate”. A wealth of studies in humans indicates that prenatal beta blockade induces long-term neurological complications including impaired school performance, cognitive impairment, and psychiatric disorders [9,10], however no studies to date have examined the long term neurological effects of acute or chronic beta blockade in one to two year old children.

Extensive animal model data from the 1980’s and 90’s reveal that beta adrenergic signaling performs diverse roles in neurological function and that beta blockade in neonates induces long lasting neurological side effects. Data published by Slotkin et al. [11] suggest that regulation of beta adrenergic signaling in the developing brain differs substantially from the homeostatic mechanisms seen in maturity, and that beta blockade in the neonate induces heterologous sensitization leading to sustained and enhanced responses to the treatment. These authors suggest that the inability of neonatal neural tissue to desensitize to beta adrenergic responses could affect neural cell development. Prenatal or postnatal modulation of beta adrenergic receptors with beta blockers affects the long term levels of the noradrenaline metabolite 3-methoxy-4-hydroxyphenylglycol (MHPG) in the frontal cortex and striatum and serotonin signaling in the frontal cortex [12-15], and induces a long term supersensitivity of the presynaptic alpha 2-adrenoceptor [16]. Postnatal beta blockade in rats less than 20 days old induced long term behavioral changes including increased time to complete the Morris’s swim test and an increase in voluntary alcohol consumption (5 mg/kg daily) [15], suggesting that acute exposure to beta adrenergic inhibitors during the rapid growth period of the cerebral catecholamine systems are related to later changes in behavior and noradrenaline signaling in the brain. Remarkably, the majority of the aforementioned studies in animal models used beta blockade doses in the 5-10 mg/kg/day range, which is only slightly more than the standard 1-3 mg/kg/day that children with IHs are commonly dosed at.

Should we continue to use propranolol as a first line treatment in children suffering from disfiguring and/or life threatening IHs? Absolutely! The efficacy of this reassigned drug far outweighs the associated acute and chronic risks. Should propranolol be used to treat cosmetic IHs? That is a question that desperately needs to be

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addressed with appropriately controlled long term studies examining the impact of neonatal beta blockade on neurological and psychological functions. In addition, clinical trials should be initiated in patients with IH examining less lipophilic beta blockers that do not readily cross the blood brain barrier such as atenolol. In the meantime, we must be diligent in ensuring that our children have access to appropriate therapies while minimizing both short and long term risks.

References


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