Inositol for the Prevention of Neural Tube Defects: A Potential Opportunity for Advocacy in Global Pediatric Neurosurgery

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Abstract:

Objective: Approximately 70-80% of neural tube defects (NTDs) are responsive to folate. Myo-inositol has increasingly been identified as a potential solution to address folate-unresponsive NTDs. We provide a brief background of existing evidence regarding the role of myo-inositol in NTD prevention and describe its role in advocacy efforts focused on NTD prevention.

Methods: A narrative review was performed.

Results: Existing data regarding the efficacy of inositol supplementation is limited by low sample sizes and primarily observational study designs. Although advocacy efforts regarding NTDs have focused on folate fortification and supplementation, examining the data for inositol intake is worthwhile. After reviewing the data, we put forth that a series of criteria would need to be met even before considering advocacy and policy. First, the weight of evidence must favor increasing inositol intake. Second, the cost-effectiveness of inositol policy must be demonstrated. Third, the policy must be politically viable. Fourth, political priority for the policy must be generated. Fifth, synergy between existing folate policy efforts and inositol policy efforts must be generated. After that series of criteria are examined, advocacy may occur through neurosurgery-specific organizations, combined approaches with other surgical disciplines, and advocacy through collaborations of various clinical and research personnel.

Conclusion: Inositol may represent an avenue for reducing the birth prevalence of folate-unresponsive neural tube defects. Given their clinical roles in treatment of spina bifida and neural tube defects, neurosurgeons are central to advocacy efforts in prevention as well.

KEYWORDS: global neurosurgery; neural tube defects; spina bifida; anencephaly; folate fortification; folate supplementation

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Introduction

Neural tube defects (NTD) are a common cause of morbidity and mortality worldwide, affecting 260,100 pregnancies worldwide annually, with an overall birth prevalence of 18.6 per 10,000 live births.[1] The birth prevalence of NTDs varies by region, ranging from 9.0 per 10,000 births in Europe to 21.9 per 10,000 births in the Eastern Mediterranean region, though the presence of a surveillance system for NTDs increases with country income status.[2] The burden of NTDs is greatest in low- and middle-income countries (LMICs).[2]

The etiology of neural tube defects is multifactorial, involving environment-gene and gene-gene influences.[3] Maternal factors include inadequate periconceptual folic acid intake, maternal hyperthermia, maternal obesity and diabetes, and use of valproate during pregnancy.[4-7] Other environmental factors include mycotoxins, pollutants, and infectious agents.[5-8]Although no Mendelian inheritance pattern has been demonstrated, NTDs may also be polygenic or oligogenic.[3, 5] NTDs also have strong genetic component, such that NTDs are more prevalent in monozygotic twins than fraternal twins and in individuals with a family history.[9] Defects in the cytoskeleton, cell cycle, and molecular regulation of cell viability have been identified in mice with NTDs.[3, 5] Transcriptional regulators and proteins affecting chromatin structure may also play a role.[3, 5] Important signalling pathways involving in the pathogenesis of NTDs include overactivation of the sonic hedgehog pathway and loss of function of the planar cell polarity pathway.[3, 5] Folic acid, inositol, and retinoic acid are involved in these pathways.[3, 5] Folate-preventable NTDs comprise approximately 70-80% of all NTDs as determined in the seminal Medical Research Council Vitamin Study demonstrating the role of folate in reducing NTDs.[10, 11] Folate resistant NTDs are thought to comprise an NTD subtype with a different etiology than those prevented with folate, perhaps owing to an inability to mediate the biological activity of folate.[12] Preventative efforts have focused primarily on increasing periconceptual folate intake among women of childbearing age to the recommended daily level of 400-800 micrograms per day.[13] Most of these efforts have occurred in high-income countries, where folate fortification is more commonly instituted and access to prenatal care is greater.[10]

While the use of folate may thus address a majority of cases of NTDs in public health initiatives, a substantial portion of NTDs are nonetheless unresponsive to folate, even with ideal use. Accordingly, it is important to understand opportunities for prevention of folate unresponsive NTDs, particularly in LMICs. Existing research efforts in this domain have focused on the role of maternal nutrition and specific nutrients. One of these nutrients, Myo-inositol, is a promising compound for which investigation has begun to address folate-unresponsive NTDs.[14] In this manuscript, we provide a brief background of existing evidence regarding the role of myo-inositol in NTD prevention. With this information and the caveat that much remains unknown regarding the role of inositol, we highlight the potential role of myo-inositol in future efforts on NTD prevention. The example of myo-inositol may also serve as an exemplar to global pediatric neurosurgery – and global neurosurgery writ large – of the need to link research to advocacy efforts.

Methods

A narrative review was performed. Searches of databases including PubMed and Google Scholar were conducted with terms including “inositol”, “myo-inositol”, “neural tube defects”, “spina bifida”, and “anencephaly.” Articles retrieved were organized thematically into description of inositol, genetic mechanisms, existing human studies, and possible role of inositol in NTD prevention efforts.

Inositol

Inositol is 1,2,3,4,5,6-hexahydroxycyclohexane, a naturally occurring six carbon sugar alcohol.[14] Of the nine stereoisomers of inositol, myo-inositol is the predominant naturally occurring isomer.[15] Adults consume 1 g of myo-inositol daily through nuts, seeds, vegetables, fruits, beans, and grains, and most tissues produce approximately 4 g per day of endogenous myo-inositol from D-glucose.[16-19] The concentration of myo-inositol in the plasma of healthy adults is 30 µmol/L due to the synergy of dietary intake, cellular uptake via Na^+ and energy-dependent co-transporters, endogenous synthesis, cellular metabolism, and clearance.[20] Myo-inositol exists as free myo-inositol, myo-inositol-containing phospholipids (phosphoinositides), or phytic acid (inositol hexakiphosphate), the latter of which is hydrolyzed mainly to free inositol prior to gut absorpion.[16, 20, 21] Myo-inositol is abundant in the brain, particularly in glial cells.[22] Inositol is a component of the intracellular phosphatidyl inositol second messenger system, which is involved in serotonin, dopamine, and glutamate receptor modulation, and is known to modulate serotonin.[23] An existing meta-analysis demonstrated that myo-inositol may be beneficial for patients with depression, particularly premenstrual dysphoric disorder.[23] Additionally, inositol has been found to regulate menstrual cycles, improve ovulation, and induce metabolic changes in women polycystic ovary syndrome and reduce the rate of gestational diabetes mellitus and preterm delivery in pregnant women.[24, 25]

Genetic Mechanisms of Inositol in NTDs

Inositol appears to act through different mechanisms than folate and is not known to directly interact with folate.[3] Studies of cultured rat embryos demonstrated that NTDs occur only in the absence of inositol.[26, 27] Similarly, inositol deficiency in the culture medium results in cranial NTDs in mouse embryos, in contrast to deficiency of folic acid.[28] The curly tail mouse strain is a multigenic model containing the major gene defect of hypomorphic allele of the grainyhead-like transcription factor 3 gene (Grhl3).[29] In this model, NTDs are unresponsive to folic acid supplementation but respond to inositol supplementation.[14] The baseline rate of NTDs is 3-7%, while inositol deficiency leads to a 70% rate of cranial NTDs.[28] Supplementation with myo-inositol or D-chiro-inositol reduces the risk in a dose-dependent manner, though D-chiro-inositol has a higher preventative capacity.[14, 20, 30] Myo-inositol may act through stimulation of protein kinase C, predominantly the beta-1 and gamma isoforms, with lower contribution from the zeta isoform.[31, 32] D-chiro-inositol may have larger downstream effects on PKC activation.[30] Incorporation of inositol into inositol phosphates and phospholipids also appears necessary to protect against NTDs in curly-tailed embryos.[31] Additionally, although inositol deficiency does not

promote incomplete posterior neuropore closure, inositol supplementation normalized closure in cultured embryos.[31] Notably, inositol is not protective against NTDs in Grhl3 null mice, perhaps due to greater severity of NTDs in the null mouse model or inositol-mediated normalization of genetic modifiers rather than Grhl3 in the curly tail model.[14, 33] Evidence of the role of inositol in NTDs has been demonstrated in human studies. Mothers of children with spina bifida have low serum myo-inositol levels.[34] The human yolk sac may be involved in the supply of myo-inositol for the developing embryo via uptake from coelomic fluid via the and endogenous synthesis.[20] The solute carrier proteins SLC2A13, SLC5A3, and SLC5A11 genes are expressed in the first-trimester placenta and yolk sac from the same pregnancy and may mediate uptake of myo-inositol, while ISYNA1 mediates the synthesis of myo-inositol.[20]

Existing Human Studies

Human studies focused on inositol have been conducted. A case-control study determined that myo-inositol was not strongly associated with the risk of NTDs.[35] The remaining four studies examined recurrence risk. The mothers in these studies were assumed to have folate unresponsive NTDs due to a history of two pregnancies with NTDs in the presence of high folate supplementation.[36] Cavalli and Copp described the case of a family that elected to receive combined treatment with 500 mg inositol and 2.5 mg folic acid daily following two previous pregnancies with NTDs.[37] A healthy baby boy was born, with no anomalous uterine contractions.[37] In two studies, Cavalli et al. presented a series of 12 mothers with a previous history of NTD-affected pregnancy who received 5 mg folic acid along with 500 mg or 1,000 mg inositol daily, yielding a total of 17 babies born without NTDs.[36, 38] The dose was 500 mg per day for the first five women but was increased to 1,000 mg following evidence indicating that doses as high as 4 g per day were safe in women undergoing in vitro fertilization.[36, 38] In total, 46.6% of mothers reported mild first trimester uterine cramps, but none experienced contractions.[36, 38] Greene et al. conducted a combined pilot randomized controlled trial and non-randomized study of women with a previous NTD-affected pregnancy.[39] Ethical standards prohibit assignment of a patient to a placebo alone when there a particular intervention has been identified as the standard of care.[14] In this case, folic acid is the standard of care. Women who were randomized to the inositol group received 1 g inositol and 5 mg folic acid, and those who were randomized to the control group received 1 g placebo and 5 mg folic acid. Among randomized pregnancies, 1 of 19 pregnancies in the placebo group experienced a NTD recurrence, compared to 0 of 14 pregnancies in the myo-inositol group. Among 22 non-randomized pregnancies, there were 2 NTD recurrences in women who took only folic acid during pregnancy and none in the inositol group. Although existing evidence is limited, women at risk for folate-unresponsive NTDs consuming inositol during the periconceptual period until late pregnancy have healthy newborns without major complications related to inositol.[40] At present, no recommended dose of inositol has been determined. However, doses as high as 18 g per day have not been associated with major side effects.[14] A minority of patients report flatulence or diarrhea.[14]

Possible Role of Inositol in NTD Prevention Efforts in Pediatric Global Neurosurgery

The field of global neurosurgery has arisen to address the global burden of neurosurgical disease by mobilizing practice, research, policy, advocacy, and education at the intersection of neurosurgical care and public health.[41-43] Pediatric neurosurgeons in high-income and upper-middle-income countries account for 85.6% of all pediatric neurosurgeons.[44] In low- and lower-middle income countries, 330 pediatric neurosurgeons care for 1.2 billion children.[44] Given the low density of pediatric neurosurgeons in these contexts, advocacy efforts focused on prevention are essential. Neurosurgeons play an important role in advocacy efforts given their wide breadth of knowledge, the importance of prevention, and the substantial personal and professional social networks.[4] Advocacy may occur through neurosurgery-specific organizations, combined approaches with other surgical disciplines, and advocacy through collaborations of various clinical and research personnel.[45] NTDs represent one of the main foci for pediatric neurosurgical advocacy.[46]

Although advocacy efforts regarding NTDs have focused on folate fortification and supplementation, advocacy for increasing inositol intake is worthwhile, provided that a series of considerations are met.[45] First, the weight of evidence must favor increasing inositol intake. The evidence basis may be divided into evidence for specific interventions and evidence supporting public health approaches.[45] At present, evidence regarding the effect of inositol in preventing NTDs is limited, though existing evidence demonstrates no increase in risk of adverse pregnancy outcomes.[14] Evidence for implementing policy to increase inositol intake is nonexistent. As evidence demonstrating the utility, or lack thereof, of inositol continues to accrue, it will be important for stakeholders to consider the role of inositol in preventing NTDs. If strong evidence demonstrating the protective effect of myo-inositol accumulates, then advocacy for increasing the intake of inositol among women in the periconceptual period and during pregnancy through policy action will be appropriate. At this point, many of the lessons learned from folate policy would be applicable. Culturally sensitive, contextually specific educational campaigns involving the government, professional organizations, and individual physicians should be initiated to increase public awareness of inositol.[4] Mandatory fortification is preferred to voluntary supplementation efforts given mandatory fortification ensures a baseline level of the nutrient and avoids limitations on efficacy due to inadequate knowledge or unrealistic perspectives often seen with supplementation policies.[4] Fortified foods must be staple foods of the local diet and be fortified with a sufficient quantity of inositol.[4] Lastly, these efforts must be coupled with widespread public health efforts to improve healthcare infrastructure and prenatal, maternal, and pediatric health [4]

Implementing inositol into public health policy requires key steps. First, the efficacy of policy action must then be evaluated. Second, the cost-effectiveness of inositol policy must be demonstrated.[45] Cost analyses, either real-world or modelled, may be the most important determinant of whether a policy is implemented in some cases. Third, policy must be politically viable.[45] The specific, measurable, attainable, relevant, and time-based

(SMART) goal framework may guide the generation of politically viable policy.[45] Policies with concentrated benefits and diffuse costs are most politically attractive.[47] Fourth, political priority for the policy must be generated.[45] Inclusion of relevant stakeholders, such as the scientific community, policymakers, economists, patient support organizations, and lay public, is central.[48] Policies must also be made sufficiently transparent.[49] Fifth, synergy between existing folate policy efforts and inositol policy efforts must be generated. The involvement of neurosurgeons in folate policy is increasing.[50-52] Combining advocacy for inositol policy with that focused on folate policy may streamline and organize neurosurgical advocacy efforts. The high bar needed for advocacy efforts obviously has not been reached: the intention of this narrative review is to raise awareness of this topic of inositol in the global neurosurgery community.

Conclusion

Inositol may represent an avenue for reducing the birth prevalence of folate unresponsive neural tube defects. Given their clinical roles in treatment of spina bifida and neural tube defects, neurosurgeons are central to advocacy efforts in prevention as well. We provide a review focused on inositol intake for the periconceptual period through late pregnancy.

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