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Statistical Versus Clinical Significance for Infants with Brain Injury: Reanalysis of Outcome Data from a Randomized Controlled Study

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Abstract

By adopting more appropriate statistical methods to appraise data from a previously published randomized controlled trial (RCT), we evaluated the statistical and clinical significance of an intervention on the 18 month neurodevelopmental outcome of infants with suspected brain injury. The intervention group (n = 32) received extensive, individualized cognitive/sensorimotor stimulation by public health nurses (PHNs) while the control group (n = 30) received standard follow-up care. At 18 months 43 infants remained in the study (22 = intervention, 21 = control). The results indicate that there was a significant statistical change within groups and a clinical significance whereby more infants in the intervention group improved in mental, motor and neurological functioning at 18 months compared to the control group. The benefits of looking at clinical significance from a meaningful aspect for practitioners are emphasized.

Keywords

newborn brain injury statistical; clinical significance

Current data suggest that 2 to 5 of 1,000 live births experience brain injury and approximately 20 to 30% of those infants develop significant neurological impairments (Ferriero, 2005; Inder, 2006). Although the incidence may seem low, the resulting impact on the child, family and society presents a formidable challenge to health professionals. Preterm and ill term infants are both at risk for sustaining brain injury although the mechanisms vary and the neurological impairments sustained depend on the extent, nature and location of the injury, as well as gestational age at the time of insult (Carli, Reigler & Evans, 2004; Inder, 2006). Neonatal brain injury occurs most frequently after a hypoxic- ischemic insult before or after birth, however, recent developments in neuroimaging and diagnostic laboratory techniques have noted that the causes are protean (Badr, 2006, Ferriero, 2005). As such brain injury or newborn encephalopathy is defined as a syndrome of disturbed neurological functioning in newborns causing long term neurological impairments such as cerebral palsy, mental retardation and seizures (Perlman, 2006)

Developmental and supportive care interventions aimed at ameliorating the negative consequences of brain injury are based on similar interventions with preterm and/or high risk infants. While most such interventions, whether using stimulation, developmental support or physical therapy have for the most part, been shown to be beneficial for high risk infants (Aucott, Donohue, Atkins & Allen, 2002; Blauw-Hospers & Haders-Alga, 2005, McCormick

et al, 2006; Symington & Pinelli, 2006, Sizun & Westrup, 2003), the efficacy of similar interventions on infants with brain injury are limited. This is rather disconcerting considering the malleability or neuroplasticity of the newborn brain confirmed more than three decades ago using rat models. In the classical rat experiments, rats maintained in an environmentally enriched environment had heavier cerebral cortices and increased brain levels of acetylcholine compared to rats reared in impoverished environments (Bennett, Rosenzweig Morimoto, & Herbert, 1979). More recently, enriched environments have also been noted to attenuate cell genesis after ischemia in adult rats (Komitova & Eriksson, 2005; Nygren, Weiloch, Pesic, Brindin & Deierborg, 2007). In humans, developmental and stimulation programs for brain injured infants have not been found to be similarly effective. A total of seven studies were found in the literature the majority of which report limited significant results (Badr, Grag & Kamath, 2006; Bao, 2005; Boyce, Smith, Immel, Casto & Escobar, 1993; Rothberg, Goodman, Jacklin, & Cooper, 1991; Nelson, et al., 2001; Ohgi, Fukuda, Akiyama, & Gima, 2004; Piper et al, 1986). This limited number of studies despite the significance of the problem is most likely due to the low incidence of infants with brain injury, the difficulty in diagnosing the timing and severity of brain injury and the irreversible brain damage that occurs, leaving little room for improvement (Butler et al., 1999, Shankaran & Laptook, 2003). Therefore, the goal of this study was to look at the benefits of intervention in a different light. The efficacy of the program is assessed across time (within groups) rather than between groups and the clinical and social significance of the intervention on infants with suspected brain injury is evaluated.

A study which used auditory-tactile-visual-vestibular intervention on 37 infants with severe central nervous system injury began in the NICU and continued for two months after discharge found no significant differences between groups albeit, the infants in the intervention group had better Bayley mental and motor scores at 12 months (Nelson, et al., 2001). An earlier study by Piper and colleagues (1986) failed to find any positive effects of an early neurodevelopmental treatment (NDT) by a physical therapist on 134 infants who had experienced birth asphyxia or were premature. The intervention, which included parental teaching, positioning and stimulation for 12 months, did not significantly alter the neurodevelopmental outcome of infants as measured on the Wilson Developmental Reflex Profile, the Milani-Comaretti Motor Development screening test or the Griffiths Mental Development Scale for the group who had birth asphyxia although positive gains were noted for the premature group. Likewise, there were no differences in the developmental quotients of 80 very low birth weight infants (half of whom were neurologically impaired) assigned to a NDT for one year at 1 year or at 6 years of age (Rothberg, et al., 1991). A study using an individualized sensorimotor intervention at three months after discharge on 58 medically fragile infants, some of whom had intraventricular hemorrhage, followed by an intervention based on the Curriculum and Monitoring System (CAMS) at 18 months also failed to show any benefits of the intervention at 30 months. This latter study assessed children on the Batelle Developmental Inventory, the Stanford-Binet Scenning Screening Test and Toddler Temperament Scale (Boyce, et al., 1993). Lack of positive effects in a RCT with 62 infants with suspected brain injury using home based individualized sensorimotor intervention for 12 months after the discharge of infants from the NICU were also reported by Badr, Grag & Kamath, (2006). The main findings of this study was that there were no differences between the intervention and the control groups on the Bayley mental and motor development scores of infants at 18 months corrected age.

On a more positive note, two studies one in Japan and one in China reported positive results. A study in Japan (Ohgi, et al., 2004) used developmental support on a group of 23 high risk infants with cerebral injuries. At 44 weeks post-conceptual age, infants in the intervention group (n = 12) had significantly better behavioral scores and higher Bayley scores, albeit not significantly higher, than the control group. A study in China on 1053 premature infants some with hypoxic ischemic encephalopathy and postnatal asphyxia found that the early intervention

group where parents were instructed to cultivate their infants' cognitive, language and motor skills had less incidence of cerebral palsy than the control group (Bao, 2005).

The lack of benefits in most studies of infants with brain injury have been attributed to methodological flaws, as well as to gaps in knowledge related to the pathology and accurate diagnosis of brain injury (Shankaran & Laptook, 2003). Specifically, most studies suffer from small sample sizes, differential attrition, the initiation of treatment after the adverse event, or after discharge (the duration of the therapeutic window is still not precisely known for human infants), no attention to clinical or social significance, lack of monitoring of the actual intervention by parents, and the fact that there is no pure control group as most high risk infants by law receive one or another form of early intervention.

Based on the above reflections, the goals of this study were to assess data from a RCT (Badr et al, 2006) using a different approach in order to: 1) evaluate the benefits of the intervention within subjects over time for infants suspected with brain injury, 2) examine the clinical significance of the intervention, and 3) evaluate the social significance of the intervention to mothers.

Clinical researchers often testify to the "meaningful" impact of the intervention on clients although a statistical significance may not have been reached. On the other hand, many studies report statistical significance but little is recounted regarding the benefit to the individuals who received the intervention. Based on these observations, the concept of "clinical significance" is gaining impetus in clinical trials (Atkins, Bedics, McGlinchey & Beauchaine, 2005; Ogles, Lunnen, & Bonesteel, 2001). Traditionally, "clinical significance" is defined as a return to "normal functioning" following treatment and a positive change for a specific individual that is not attributed to chance (Jacobson & Traux, 1991; Jacobson, Follette, Revenstorf, et al. 1984). Jacobson and colleagues defined clinical significance by two criteria: 1) the magnitude of the change has to be statistically reliable and b) by the end of treatment, the subjects should end up in a range of the normal population; or that their scores following treatment fall closer to the mean of the normal population. It is worth noting that, a return to normal functioning is not a possible criterion to apply to some clinical populations (Cisler, Kowalchuk, Sunders Zweben & Trinj, 2005; Gaudiano 2006), such as in our sample of infants, who were suspected to have brain injury after birth. In such a situation, it may be more appropriate to define a clinically significant change according to a standardized level of improvement (Jacobson & Traux, 1991), which is what we employed in this study. Social significance as defined by Kazdin (1999) is the extent to which an intervention makes a "real" difference in the everyday life of an individual. The importance of social significance is also gaining recognition in clinical research due to its practical relevance to outcomes. There are no published studies to date on clinical or social significance of intervention in high risk infants or those with suspected brain injury.

The theoretical basis for looking at clinical significance is the fact that when clinicians rely solely on significant p values to look at differences between groups, they fail to discern changes over time, to assess variance, to examine the direction of a treatment effect, and to monitor the value of the treatment on an individual or a society (Bhandari, Montor & Schemitsch, 2005; Guyatt et al. 2003, Gaudiano, 2006; Shakespeare et al. 2001, Sterne, 2002; Wright et al., 2003). Furthermore, in many published studies a non-significant result ($p > 0.05$) could be due to factors such as a small sample size (type II or beta error), which is common in studies with brain injured infants where there are few cases to be studied, and not a reflection of the lack of efficacy of the intervention itself. Given the expense, time and effort in designing and implementing RCTs and with the limited number of infants with brain injury, it is crucial that data be assessed for the maximum positive value. Based on the above the questions to be answered in this study were the following:

1. What are the changes in the Bayley scores for infants within each group?
2. What is the clinical significance of the intervention using two methods: a) the magnitude of change over time in the mental and motor functioning of infants, that is a change of more than 2 SD or +30 points change on the Bayley assessment scales and b) a 20% reduction in abnormal neurological findings or a change a 20% or more in the status of infants from an abnormal neurological examination to a normal neurological examination 3) What is the social significance, or the extent to which mothers deemed the intervention beneficial for them and their infants?

Methods

Study Design

The original study was a randomized control trial (RCT), repeated measure design looking at the efficacy of intervention between subjects in the control group versus the intervention group. The present study looked at the differences “within” subjects and tested the clinical and social significance of a home-based cognitive and sensorimotor intervention.

Setting

The study was conducted in the homes of infants who were diagnosed with brain injury before discharge from four hospitals in Southern California. Institutional Review Board (IRB) approval was obtained from all hospitals that agreed to participate in the study. Informed consent was obtained from all parents who agreed to participate in the study.

Subjects

The initial total sample consisted of 62 families with infants suspected of having sustained brain injury. Infants were randomly assigned to a control ($n = 30$) and an intervention group ($n = 32$). Power analysis for two independent groups based on the between-group means and standard deviations of previous studies using the Bayely scores (eg. Badr et al, 2006) note that 20 infants per group will be necessary for 95% power to detect the effect of intervention on the Bayley scores. ($p = .05$, two-tail). Infants were recruited when they met the following criteria: 1) Occurance of a brain injury based on the criteria established by the University of California at San Francisco group studying brain asphyxia (Miller et al, 2002), 2) abnormal findings on a neurological examination by the neurologist at each facility (performed as soon as brain injury was suspected within one or two days after birth) 3) an abnormal MRI or EEG and 4) birth after 28 weeks gestation (Badr et al, 2006). Mothers were between 17 and 40 years of age, from different socioeconomic and ethnic backgrounds, and willing to participate actively in the intervention if they were in the experimental group. Infants were excluded if they had Grade IV intraventricular hemorrhage (IVH) with periventricular leukomalacia or evidence of severe cortical destruction or atrophy. Exclusion criteria were based on the severe long-term consequences and higher mortality rates for infants with these conditions, and on the questionable benefit of intervention (Nelson et al, 2001; Shankaron & Laptook, 2003). At 12 months corrected age, 47 infants remained in the study (24 intervention and 23 control) and at 18 months corrected age, 43 infants remained in the study; (23 intervention and 20 control) 2 died, 3 were dropped from the study due to non-compliance with the follow-up visits, and 14 (23%) were lost to follow-up. Although efforts were made to minimize attrition such as developing bonds with the family, collecting addresses of extended family, neighbors and friends, being flexible in time and place of visit, calling the families frequently, and empowering and supporting parents during the visits ⁽⁴⁶⁾, the 23% attrition rate is a limitation to the study and one of the shortcomings identified in earlier studies with this population. Nevertheless, the characteristics of the families (eg. education, ethnicity) and infants (eg.

Bayley scores and neurological examinations at baseline) who remained in the study were not different from those lost to follow-up.

The Intervention—The intervention used the Curriculum and Monitoring System (CAMS) method which consists of mental and sensorimotor stimulation (CAMS, 1992). The CAMS has been used by researchers at Utah State University (Casto & White, 1993) and was selected for this study because it was the only one available at the time with promising results and for high risk infants. The CAMS which was taught to mothers by trained public health nurses (PHNs) consists of five areas: cognitive, language, motor, self-help, and social skills with more than 100 defined and illustrated activities aimed at enhancing development of children from birth to 5 years. Although very specific and detailed, the CAMS was individualized based on the progress of each child and the needs of each mother. The PHNs recorded how many minutes mothers provided the intervention and coached them to adhere to daily 20-minute stimulation activities. In addition to teaching CAMS, the PHNs supported and empowered mothers in the care of their infants.

Outcome Measures—The research assistant (RA) who was blinded to group assignment and the hypotheses of the study was trained to an inter-reliability score of at 90% with the Principal Investigator (PI). The RA visited the mothers in their homes at discharge from the NICU, and at 6, 12 and 18 months corrected age where she performed the Bayley assessment scales

Motor and mental development

The second edition of the Bayley scales of infant development (BSID) were used (Bayley, 1993). The BSID consists of three scales (mental, motor, and behaviour) that are used to assess development in young children aged 15 days to 42 months. The test was standardized in the United States with a representative sample of 1,700 children. Standard scores are derived from the results with a mean of 100 and a standard deviation of 15. The mental scale (MDI) reflects language and perceptual development and the motor scale (PDI) reflects gross and fine motor development. The BSID are the most widely used standardized measures of cognitive and motor development in infancy and early childhood and the psychometric properties of the instrument are reportedly high for all scales. Reliability coefficients for the MDI range from .78 to .93 and for the PDI ranges are from .81 to .91. (Bayley, 1993, Provost et al. 2004).

Neurological examinations

Neurological examinations were performed by one experienced pediatric neurologist at UCLA and who was blinded to the study hypotheses and the clinical course of the infants. The assessments were done at four points in time: at baseline, at 6, 12 and 18 months corrected age. The neurological exam recorded items such as head tone, limb tone and movement, reflexes, developmental delays, vision and hearing problems, and head size, and was classified as either normal or abnormal.

Procedure—Infants were recruited from four Los Angeles Regional Centers after they had been diagnosed with brain injury and after their parents signed the consent form. Infants were randomly assigned to an experimental group or a control group. Trained PHNs visited the experimental families twice a week for one month, every week until the infant was 4 months of age and then every other week until the infant was 12 months old, they taught the parents (mostly mothers) how to apply the CAMS to their infants and they provided support and encouragement to mothers. Parents in the control group did not receive any special training or visitation by trained PHNs however; they received the standard care provided by the Los Angeles regional centers. One trained research assistant blinded to group assignment visited

all families at home for data collection. Families were requested to bring their infants to the UCLA clinics for the neurological assessments.

Statistical Analysis

Summary statistics of all variables at each of the four time points were obtained. For statistical significance the two-way repeated measure ANOVA was used to detect changes in the Bayley scores from 6 months to 18 for each group (within group) {the 6 months scores were used for baseline in the analysis instead of the baseline assessments since earlier scores are not very accurate for high risk infants,(Koseck & Harris, 2004)}.

For clinical significance, the *magnitude of change* was calculated for each infant using 2 criteria: 1) the percent of infants whose scores improved 2 SD on the Bayley tests or a 30 point improvement and 2) a 20% return to normal functioning on the neurological assessments, that is a change from an abnormal neurological examination to a normal neurological examination (Brandon, 2006; Jacobson et al 1999). Wilcoxon signed Ranks test was used to look at the differences between groups on the BSID scores and the neurological examinations. For social significance the mothers were asked by the RA whether they thought the intervention was beneficial of them and their infants using a yes no answer (Foster & Mash , 1999; Kazdin, 1999; Kendall, 1999).

Results

The characteristics of the sample are noted in Table 1. Sixty-eight percent of the sample was of Hispanic origin, which reflects the birth rates of Los-Angeles, and 60% had prenatal care in the second trimester. Although randomization was used, the experimental group had lower APGAR scores at 5 minutes, albeit not significant ($p = 0.07$). All other background and intervening variables of experimental and control groups showed no differences between groups. Eleven infants (6, intervention & 5 control) manifested abnormal neurological findings at 12 and 18 months. Abnormal findings included hemiparesis, hemiplegia, decreased muscle tone, scissoring, choreoathetosis, microcephaly, decreased vision and spastic cerebral palsy.

Within Subject Statistical significance

Comparisons of infants in each group for changes in the BSID scores between 6 months and 18 months on the ANOVA revealed a significant decline in the mental scores of infants in the control group (see Figure 1); the mean MDI score at 6 months was 92.5 ± 17.3 which declined to 79.5 ± 15.4 at 18 months ($F_{2/39} = 4.54, p = 0.03$), whereas there was no similar significant decline for the intervention group (mean score of 84.5 ± 13.2 at 6 months and which declined to a mean score of 81.8 ± 12.4 at 18 months ($F_{2/39} = 1.56, p = 0.14$). In contrast, the motor scores showed a significant positive increase for the experimental group which changed from a mean of 79.3 ± 20.4 at 6 months to a mean of 83.1 ± 18.5 at 18 months ($F_{2/39} = 4.46, p = 0.03$). The control group also increased from a mean of 83.6 ± 22.5 at 6 months to a mean of 86.2 ± 17.3 at 18 months but that change was not significant ($F_{2/39} = 1.54, p = 0.29$), (see Figure 2).

Clinical significance

Change on the Bayley scores: Comparison of the 2 groups using the magnitude of change or an improvement of 2 SD or + 30 points towards normal functioning revealed that for the intervention group, 29.3% of the infants showed an improvement at 18 months on the MDI scores, 48.3% remained unchanged while 22.4 % deteriorated. For the control group; 18.4% improved, 44.9% remained unchanged 36.7 % deteriorated. Based on Wilcoxon Signed Ranks Test the difference between groups is significant at $z = 4.91, p < 0.05$. For the PDI scores, in

the intervention group 44.3%, improved 37.3% remained unchanged and 18.4 deteriorated. In the control group 33.4 improved, 29.9 remained unchanged and 36.7% deteriorated $z = 6.26$, $p < 0.01$.

Improvement in Neurological assessments—At 18 months corrected age, the number of infants in the intervention group who had abnormal neurological examinations dropped from 22 out of 32 infants (69%) at baseline to 6 out of 23 (26%) at 18 months, this represents a 43% return to normal functioning. In comparison, the control group had 15 out of 30 (50%) infants with abnormal neurological examinations at baseline which decreased to 5 out of 20 cases (25%) at 18 months, which represents a 25% return to normal functioning. Thus, the clinical improvement for the intervention group was almost twice that for the control group, a significant difference of $Z = 2.12$, $p = 0.033$ using Wilcoxon Signed Ranks tests.

Social significance

Interventions have little chance of succeeding if the caregiver finds them arduous or they are unwilling to implement them. In our study, 87% of mothers in the intervention group reported their satisfaction with the care provided by the PHNs and indicated that the intervention was beneficial for them and their infants which is in accordance with the definition of social significance as “the extent to which treatment goals, procedures, and outcomes were considered beneficial by the mothers”. Most mothers in the intervention group became attached to the PHNs, were weary of ending the home visitation and indicated that the PHNs were helping them in the care of their infants in providing formal support. For the control group satisfaction with care the routine care provided was at 65%.

Discussion

Our findings suggest that examining changes within groups over time, as well reporting clinical and social significance, rather than relying exclusively on differences between groups which may be affected by numerous factors is essential. This is rather crucial when clinicians and health providers are establishing what is meaningful or important in study results and when planning future interventions. To date researchers are still unclear as to what constitutes a clinically meaningful intervention aimed at enhancing the development of infants suspected of brain injury at birth. Most studies which attempted rehabilitation for infants with brain injury have not found statistically significant results, yet one should look at several factors which may have affected outcome; one possible explanation is that many studies have not assessed long-term development, which if done may have shown a positive effect. Another possible factor is the small number of subjects in many studies with brain injured infants which could lead to a type one error which in reality may not be noted if the sample size was larger.

Another explanation which we had put forth earlier (Badr et al, 2006) and which may well be validated by the positive impact of interventions noted in international studies (eg. Bao, 2004; Ohgi, Fukuda, Akiyama, & Gime, 2004; Zhou et al, 2002) is the lack of a pure control group in studies conducted in the United States. Due to ethical concerns and the fact that all high risk infants in the United States are eligible for intervention, one may not find a true effect due to additional intervention provided in clinical trials. Replicating similar intervention studies in other less developed countries where unfortunately no intervention is available for high risk infants, researchers may be able to assess the factual long term benefits of the intervention.

Another argument put forth in the present paper, and that may raise debate is the clinical and social significance of intervention. We did not find a significant difference between groups in the original study probably due to the small sample size, the high attrition rate, and the possible disparity between the families all of which render the detection of significant effects

improbable. Nevertheless, twice as many infants returned to normal neurological functioning in the intervention group as did the control group and more infants in the intervention group improved in their motor function than in the control group. If we had not looked at clinical significance, these results would have been missed. A clinical significance for one single parent or child may be much more important than a statistically significance test or a correlation between measures (Kazdin, 1999).

It is worth pointing that the statistical and clinical improvement noted in this study for the intervention group could be due to the interveners rather than the intervention, a argument which has been well debated in the literature (de Souza et al. 2006). Infants in our study, both in the intervention and the control groups, experienced a decline in their mental scores and an increase in their motor scores. This unexpected finding was recently debated by Green and colleagues (2006) who noted that the negative correlations between cognitive and motor functions, as noted in our study, may be a trade-off or competition between the functions for restricted neural resources during recovery.

The findings of this study may be of interest to health providers and caregivers. Interventions that result in improved motor development for infants with brain injury, or that show significant improvements in neurological functioning, represent effects that serve critical interests in both the personal and public health domains. Such outcomes have potentially far-reaching consequences for promoting the health and development of infants who are affected by a perinatal brain injury and who are likely to develop significant neurological and developmental impairments.

Parental satisfaction with treatment is to be acknowledged since several researchers have documented that compliance with an intervention is more likely to occur if parents look favorably at the intervention and the intervener (Cameron Maehle & Reid, 2005; de Souza, Sardesai, Joshi, Joshi & Hughes, 2006). This could be an important fact to consider in upcoming intervention studies since client perception of the intervention may be critical in determining efficacy (Kazdin, 1999).

Unfortunately, the limitations of this study are similar to those identified in earlier ones; small sample size and possible differential attrition. Although every attempt was made to keep in contact with families in order to limit attrition, 23% of our sample was lost to follow up. It is possible although not likely based on the baseline data available and the interest expressed by the majority of the families in continuing to have their infants monitored by the study personnel, that those lost to follow-up may have experienced additional stressors or that their infants may have manifested additional problems such that they could not be further involved in the study.

Future research is recommended to look at reliable clinical significant outcomes of intervention studies aimed at enhancing the neuro-developmental outcomes of infants with brain injury and to link a special intervention to a specific outcome. An intervention that promotes motor functioning may not result in improved mental functioning. In addition, clinical significance is not yet very well defined among researchers and needs to be further studied especially considering that various approaches exist to detecting meaningful change (Bauer, Lambert & Nielsen, 2004; Ogles, Lambert, & Sawyer, 1995).

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Figure 1.
Bayley mental scores for the three time periods

Figure 2.
Bayley motor scores for the three periods

Table 1

Characteristics of the sample

Characteristic	Control (30) Mean SD	Experimental (32) Mean SD	Wilcoxon <i>p</i> -value
Birth weight	1882.83 ± 1393.42	1538.41 ± 893.34	0.74
Gestational age	30.98 ± 2.06	30.03 ± 2.72	0.72
APGAR score-1 min	6.09 ± 1.98	4.82 ± 2.69	0.11
APGAR score-5 min	7.74 ± 1.39	6.64 ± 2.22	0.07
Male to female ratio	18/12	20/12	0.84
Prenatal care in the 2nd trimester	18 of 30	25 of 32	0.20
Maternal age	25.41 ± 1.04	29.1 ± 1.2	0.05
Maternal education: Grade 12 or more	18 of 30	17 of 32	0.77
Days in hospital	69.5 ± 9.03	57.8 ± 5.2	0.76
Hispanic (n)	21	22	0.92 ^(a)
Caucasian (n)	3	4	0.76 ^(a)
African America (n)	3	4	0.76 ^(a)
Other ethnic group (n)	3	2	0.94 ^(a)

^(a) Note that these Chi-Square test *p* values should be used with caution since the counts were low (less than 5)