QUESTION 2: PROTOCOL

32102717

Abstract

We propose a double-blind, randomised, placebo-controlled study of Vinpocetine for increasing IQ points, as measured on the Wechsler Adult Intelligence Scale. Vinpocetine is a vasodilating agent known to increase blood circulation in the brain [5;7]. We will measure the change from baseline of IQ after 28 days of receiving 10mg of Vinpocetine daily. Block randomisation with multiple block sizes will be utilised. Our clinically relevant difference between the placebo and test groups will be 10 IQ points, in a population of healthy individuals aged 18-64 years. Our primary analysis will be ANCOVA, and we estimate a required total sample size of 88 individuals, and 65 days to complete the study. We aim to answer the question of whether Vinpocetine can increase IQ.

---

1. Background

Vinpocetine is a vasodilating agent known to increase blood circulation in the brain [5;7]. Discovered in the late 1960s, it is derived from the Lesser Periwinkle plant [9], and evidence has been found to suggest Vinpocetine has positive effects on the memory [7;8]. There have also been investigations into the effect of Vinpocetine in the treatment of organic psychosyndrome [3], cognitive impairment and dementia [9], chronic vascular senile cerebral dysfunction [2], and many other areas. There are, however, no studies that investigate the ability of Vinpocetine to increase IQ.

2. Study Goals and Objectives

During this study we are aiming to investigate whether Vinpocetine can increase IQ by increasing blood flow to the brain. Our main objective is to investigate the question: Does taking 10mg of Vinpocetine daily for 28 days increase IQ in a subject (as measured on the Wechsler Adult Intelligence Scale (WAIS)) by atleast 10 points.

3. Methods

3.1. **Study Design.** We will be implementing a placebo-controlled trial, since there is currently no standard treatment for increasing IQ. The placebo-control will be identical to the test treatment, Vinpocetine, in every way, except that it will not include the active agent. Double blinding will be used, such that neither the investigator nor the subject will know which treatment the subject is on. This will be ensured by the dummy placebo treatment. To assign patients to groups we will utilise block randomisation. We have two groups, treatment and placebo, and so our block size will be a multiple of 2. To protect the block size from being revealed we will use a random block size selected from $(2, 4, 6, 8)$ each time a block is drawn, thus the largest imbalance of the groups will be 4. With a required sample size of 88, as calculated in §3.4, this imbalance is acceptable. We do not intend to adjust for any confounding for variables such as age or sex, and thus do not feel the need to balance the groups for these variables through an alternate randomisation method such as stratified randomisation or minimisation with a random element. The study will be multi-centre in order to aid recruitment and to ensure diversity and generalisability within the study population. Our primary end point will be a 95% confidence interval for the difference between the two group mean follow-up IQ scores (measured on the Wechsler Adult Intelligence Scale), after receiving 10mg of Vinpocetine daily for 28 days, adjusted for possible baseline imbalance.

3.2. **Study Population.** We are aiming to recruit 88 patients across a total of 10 centres, as calculated in §3.4 and discussed in §3.3. There are no previous studies for which to match our sample population to ensure comparability of studies. We aim to make the population generalisable, thus we wish to include both male and female patients between the ages of 18-64 years, any races or ethnicities, native English speakers, with no previous experience of taking drugs that are intended to increase IQ. We will not include patients outside the given age range

(i.e. children), pregnant women, any patients with medically diagnosed memory issues or impaired mental capacity, or any patients currently taking medication that could affect their memory (either directly or through side affects). Any other inclusion or exclusion criteria are subject to the clinicians judgement. We will acquire informed consent from the patients through the standard methods (a consent form), in line with the guidelines of the Declaration of Helsinki [1]. We aim to ensure access to the study population through utilising a multi-centre study, and our main methods of recruitment will be through advertisements, fliers, word of mouth, and GP surgeries.

The study will have the limitation that it cannot be compared to historical data of previous similar studies, as none exist. Our only ethical concern is whether the study is necessary, given there is no obvious medical application for a treatment that increases IQ. We will need to confer with the clinician about this concern.

3.3. **Study Procedures.** Each patient in the test group will receive 10mg of Vinpocetine to be taken daily on each day of the study period. The clinician has not explicitly stated the the duration of the study period for each patient, as discovered in Phase II of this trial, nor the medium through which the 10mg of Vinpocetine will be taken. For the purpose of this document, we will assume that 10mg tablets of Vinpocetine are to be taken daily for a period of 28 days (4 weeks), to be confirmed with the clinician.

During the study we will be aiming to determine if 10mg of Vinpocetine taken daily for 28 days increases IQ by atleast 10 points. To measure IQ we will utilise the Wechsler Adult Intelligence Scale (WAIS). The WAIS works by measuring abilities in four main categories; reasoning, retention of information, processing and organization of information, and verbal comprehension [11]. We were unable to locate a reference that describes who the WAIS was validated on, but we will assume healthy adults with no diagnosed cognitive issues, and will confirm with the clinician. This is supported by the fact that the WAIS is widely used and attempts have been made to validate it for other populations [6;10].

We will take a baseline measurement of IQ for each patient at the beginning of their study period, and a follow-up measurement of their IQ will be taken on either day 28 of their study period, after they have taken their final dose of Vinpocetine, or on day 29, depending on what the clinician advises. We may also collect information on patients age, sex, race, education history, and any other confounding variables the clinician may suggest, to accommodate possible secondary analyses. Multiple follow-ups throughout the study period could be considered, in order to gain a greater picture of how Vinpocetine affects IQ over time, however there are many issues with this. The most prominent issue is that it will likely cause high levels of drop out, as patients will not want to regularly keep returning to do tests, so this procedure was not implemented. We will confer with the clinician to ensure the attending staff are adequately trained and available in sufficient numbers throughout the trial.

The duration of the trial will depend on the rate of capture, how many centres are used, the required sample size, and how long each patient remains on the treatment. Assuming that we utilise 10 centres, each having a capture rate of 2 consenting patients who fulfil the inclusion criteria per week (7 days), a required sample size of 88, as calculated in §3.4, and each patient being on the drug for 28 days, we will need a trial duration of $\left(88 \div \frac{10\times 2}{7}\right) + 28 \approx 31 + 28 = 59$ days. We can then add a 10% buffer to this estimate to adjust for rate of capture decline or overestimation, bringing the trial length up to 65 days. There is also the possibility of adding additional centres or sample size recalculation during the study (without breaking blinding). The parameter estimates in this calculation will depend on the clinicians beliefs, but we can demonstrate how robust the estimates are; if we increase the number of centres to 20 then the base trial length becomes 44 days. If instead we change the rate of capture per centre to 8, then the base trial length becomes 36 days. Alternatively if the length of time each patient is on Vinpocetine is 56 days then the base trial length becomes 87 days.

3.4. **Sample Size Calculations.** Sample sizes for the study need to be calculated before the study begins to ascertain if it is feasible to acquire the necessary number of patients in order to guarantee the desired power. If these calculations are underestimated then the study may not

have sufficient power to detect differences between the two groups. We will now demonstrate how the calculations are derived in the case of a Z-test for the difference of the two group means. This is an approximate calculation of sample size for a t-test of two group means, so we will then use R (Version 3.4.2) to calculate exact sample sizes for a t-test of two group means (for follow-up scores), and explain why this is an appropriate estimate of sample size for ANCOVA, adjusting for baseline.

To derive the sample size for the study we must make certain assumptions about the distributions of the response variables and their parameters. In the case of a Z-test for the difference of two group means our response variables are IQ follow-up scores in the placebo and test groups. We make the assumption that the response variables in each group are independent and identically distributed with normal distributions

$$X_{P,F} \sim \text{Normal}(\mu_{P,F},\, \sigma^2) \qquad \text{and} \qquad X_{T,F} \sim \text{Normal}(\mu_{T,F},\, \sigma^2). \tag{1}$$

The mean and standard deviation of IQ scores without intervention are taken to be known, with values $\mu_{P,F} = 100$ and $\sigma = 15$. We wish to perform a two-sided Z-test to detect a difference in the means of the two groups, $\mu_{P,F}$ and $\mu_{T,F}$, at significance level $\alpha = 0.05$ and minimum power of $1 - \beta = 0.8$, thus $\beta = 0.2$. We now let $n_P = rn$ be the number of patients in the placebo group and $n_T = (1-r)n$ be the number of patients in the test group, with $n = n_P + n_T$. We define the difference in the means to be $\Delta = \mu_{T,F} - \mu_{P,F}$, and take $\Delta^* = 10$ to be our clinically relevant difference, which we will use as our working hypothesis. We can estimate Δ using the unbiased estimator $\bar{\Delta} = \bar{X}_{T,F} - \bar{X}_{P,F}$. Since $\bar{\Delta}$ is a linear combination of two Normal random variables, the distribution of $\bar{\Delta}$ is also Normal, with mean given by

$$\mathbb{E}[\bar{\Delta}] = \mathbb{E}[\bar{X}_{T,F} - \bar{X}_{P,F}] = \mathbb{E}[\bar{X}_{T,F}] - \mathbb{E}[\bar{X}_{P,F}] = (\mu_{T,F} - \mu_{P,F}), \tag{2}$$

and variance given by

$$Var(\bar{\Delta}) = Var(\bar{X}_{T,F} - \bar{X}_{P,F}) = Var(\bar{X}_{T,F}) + Var(\bar{X}_{P,F}) = \frac{\sigma^2}{r(1-r)n}. \tag{3}$$

Thus, the distribution of $\bar{\Delta}$ is given by

$$\bar{\Delta} \sim \text{Normal}\left((\mu_{T,F} - \mu_{P,F}), \frac{\sigma^2}{r(1-r)n}\right), \tag{4}$$

Since this a superiority clinical trial, our hypotheses are given by:

$$\text{H}_0 : \Delta = 0 \qquad \text{vs.} \qquad \text{H}_1 : \Delta \neq 0 \quad \text{(working hypothesis } \Delta^* = 10). \tag{5}$$

Define the test statistic, Z, to be

$$Z = \sqrt{r(1-r)n}\frac{\bar{\Delta}}{\sigma} = \sqrt{r(1-r)n}\frac{(\bar{X}_{T,F} - \bar{X}_{P,F})}{\sigma}. \tag{6}$$

Under the null hypothesis,

$$Z \sim \text{Normal}(0, 1). \tag{7}$$

Under the alternate hypothesis,

$$Z \sim \text{Normal}(\theta^*, 1), \tag{8}$$

where $\theta^* = \frac{\Delta^*\sqrt{r(1-r)n}}{\sigma}$, where $\Delta^* = 10$ is the clinically relevant difference.

We know that power is given by $\mathbb{P}[\text{reject H}_0 \mid \text{H}_1 \text{ is true}]$, thus we can set the power equal to our target value

$$\begin{aligned} &\mathbb{P}\left[|Z| \geq \Phi^{-1}(1 - \tfrac{\alpha}{2}) \mid \text{H}_1 \text{ is true}\right] = 1 - \beta, \\ \implies &\mathbb{P}\left[Z \leq \Phi^{-1}(\tfrac{\alpha}{2}) \mid \text{H}_1 \text{ is true}\right] + \mathbb{P}\left[Z \geq \Phi^{-1}(1 - \tfrac{\alpha}{2}) \mid \text{H}_1 \text{ is true}\right] = 1 - \beta. \end{aligned}$$

It is known that $\mathbb{P}\left[Z \leq \Phi^{-1}(\frac{\alpha}{2}) \mid \text{H}_1 \text{ is true}\right] \to 0$ and $\Delta \to \infty$ and has a maximum value of 0.05 when $\Delta = 0$. Thus the above equation is approximately equivalent to

$$\begin{aligned} &\mathbb{P}\left[Z \geq \Phi^{-1}(1 - \tfrac{\alpha}{2}) \mid \text{H}_1 \text{ is true}\right] = 1 - \beta, \\ \implies &\mathbb{P}\left[Z \geq \Phi^{-1}(1 - \tfrac{\alpha}{2}) \mid \text{H}_1 \text{ is true}\right] = 1 - \beta, \\ \implies &\mathbb{P}\left[Z - \theta^* \geq \Phi^{-1}(1 - \tfrac{\alpha}{2}) - \theta^* \mid \text{H}_1 \text{ is true}\right] = 1 - \beta. \end{aligned}$$

Now using the fact that $\Phi(x) = \mathbb{P}[X < x]$,

$$\begin{aligned}
&\implies 1 - \Phi(\Phi^{-1}(1 - \tfrac{\alpha}{2}) - \theta^*) = 1 - \beta, \\
&\implies \Phi^{-1}(1 - \Phi(\Phi^{-1}(1 - \tfrac{\alpha}{2}) - \theta^*)) = \Phi^{-1}(1 - \beta).
\end{aligned}$$

Using $1 - \Phi(x) = \Phi(-x) \implies \Phi^{-1}(1 - \Phi(x)) = -x$, so

$$\begin{aligned}
&\implies -\Phi^{-1}(1 - \tfrac{\alpha}{2}) + \theta^* = \Phi^{-1}(1 - \beta), \\
&\implies \theta^* = \Phi^{-1}(1 - \tfrac{\alpha}{2}) + \Phi^{-1}(1 - \beta), \\
&\implies \tfrac{\Delta^* \sqrt{r(1-r)n}}{\sigma} = \Phi^{-1}(1 - \tfrac{\alpha}{2}) + \Phi^{-1}(1 - \beta), \\
&\implies n = \left(\Phi^{-1}(1 - \tfrac{\alpha}{2}) + \Phi^{-1}(1 - \beta)\right)^2 \frac{\sigma^2}{(\Delta^*)^2 r(1-r)}.
\end{aligned}$$

Thus an approximation of the sample side needed to perform a two-sided Z-test at significance level α to attain a power of $1 - \beta$ is given by

$$n = \left(\Phi^{-1}(1 - \tfrac{\alpha}{2}) + \Phi^{-1}(1 - \beta)\right)^2 \frac{\sigma^2}{(\Delta^*)^2 r(1-r)}. \tag{9}$$

Using our approximations of the parameters of this model, we estimate that an approximate necessary sample size for this type of analysis is 71 patients total, assuming equal sized groups such that $r = 0.5$. Using R (Version 3.4.2) we can calculate exact sample sizes needed for a two sample t-test of two group means, 37 patients per treatment group. We have a possible offset of 4 from our block randomisation, so we could have groups of 35 and 39, so we increase our sample size to 39 in each group to ensure we will always have enough participants in each group to attain the required power. This gives us a total of 78 patients required. Assuming that 10% of the patients recruited drop out, we will require $\frac{78}{0.9} = 87$ total patients, which we will increase to 88 to allow for the possibility of equal sized groups. Since our planed analysis is actually ANCOVA (adjusting for baseline) and not a t-test of the two group means of follow up IQ scores, this is just an estimate. It has been shown, however, that ANCOVA may reduce the number of patients required in a study to attain a desired power [4], and so using the higher estimate will still ensure the desired power is attained.

It may be the case that some of the estimated parameters in our sample size calculations are over- or under-estimated. We will now perform sensitivity analysis to investigate the effect of changing the parameter estimates on the sample size calculated in R (Version 3.4.2) for a two sample t-test of two group means. When we set $\sigma = (1, 5, 10, 14, 25)$ we get a base sample size of (2, 6, 17, 32, 100) patients per group respectively.

4. Data Analysis

We aim to investigate whether 10mg of Vinpocetine taken daily for 28 days can increase IQ by 10 points (as measured by the WAIS). Thus for our analysis we will be comparing the placebo group to the test group. We intend to use ANCOVA in order to compare the means of the follow-up IQ scores for the two groups, while adjusting for baseline IQ scores for each patient. We aim to produce a 95% confidence interval for the difference between the two group mean follow-up IQ scores (measured on the Wechsler Adult Intelligence Scale), after receiving 10mg of Vinpocetine daily for 28 days, adjusted for possible baseline imbalance.

References

[1] World Medical Association. Wma declaration of helsinki ethical principles for medical research involving human subjects. *World Medical Association*, 2013.

[2] Roberto Balestreri, Luigi Fontana, and Federico Astengo. A double-blind placebo controlled evaluation of the safety and efficacy of vinpocetine in the treatment of patients with chronic vascular senile cerebral dysfunction. *Journal of the American Geriatrics Society*, 35(5):425–430, 1987.

[3] L. Blaha, H. Erzigkeit, A. Adamczyk, S. Freytag, and R. Schaltenbrand. Clinical evidence of the effectiveness of vinpocetine in the treatment of organic psychosyndrome. *Human Psychopharmacology: Clinical and Experimental*, 4(2):103–111, 1989.

[4] George F. Borm, Jaap Fransen, and Wim A.J.G. Lemmens. A simple sample size formula for analysis of covariance in randomized clinical trials. *Journal of Clinical Epidemiology*, 60(12):1234 – 1238, 2007.

[5] Masatoshi Hagiwara, Toyoshi Endo, and Hiroyoshi Hidaka. Effects of vinpocetine on cyclic nucleotide metabolism in vascular smooth muscle. *Biochemical Pharmacology*, 33(3):453 – 457, 1984.

[6] Jill J. S. Jones, Paul van Schaik, and Paul Witts. A factor analysis of the wechsler adult intelligence scale 3rd edition (wais-iii) in a low iq sample. *British Journal of Clinical Psychology*, 45(2):145–152, 2006.

[7] Mark Mcdaniel, Steven F Maier, and Gilles Einstein. "brain-specific" nutrients: A memory cure? 19:957–75, 11 2003.

[8] Z. Subhan and I. Hindmarch. Psychopharmacological effects of vinpocetine in normal healthy volunteers. *European Journal of Clinical Pharmacology*, 28(5):567–571, Sep 1985.

[9] Szabolcs Szatmri and Peter Whitehouse. Vinpocetine for cognitive impairment and dementia. 1:CD003119, 01 2003.

[10] Paul van der Heijden and Jacobus Donders. Wais-iii factor index score patterns after traumatic brain injury. *Assessment*, 10(2):115–122, 2003. PMID: 12801182.

[11] Wechsler Test. Wechsler Adult Intelligence Scale. `https://wechslertest.com/about-wechsler-intelligence-test`, 2018. [Online; accessed 2018-01-27].