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A PILOT STUDY ON THE EFFECT OF PRAMIPEXOLE IN CALLUS FORMATION IN DISTAL RADIUS FRACTURES IN PERIMENOPAUSAL FEMALES

Orthopaedics

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ABSTRACT

This is a pilot study that was conducted over a period of three months in Burdwan Medical College and Hospital, on the effect of Pramipexole on distal radius fracture callus formation in perimenopausal females (40 – 60 years). There were a total of 11 patients studied during a period of 3 months. Cases were followed for 4 complete weeks following discharge after applying proper manipulation and reduction of fracture and subsequent application of plaster cast. Ultrasonography of the distal end of affected radius was utilized to estimate volume of callus formation. Two treatment arms (one with pramipexole and one with symptomatic treatment) were created and their efficacy with regard to callus formation was observed. Following cleaning of data, mean case volume was found to be two whole orders of magnitudes greater than mean control volume. Welch's T-test was subsequently carried out and showed a near statistically significant large effect size of 1.21 (p=0.055, t=2.046, right tailed). This effect size is quite large and may be taken to indicate significant clinical relevance of using pramipexole. Further studies are recommended to follow up on these results, with increased sample size, and multiple measurements of callus volume to observe the dose-callus-time relationship. In conclusion, this drug seems a promising cost-effective way to augment and speed up callus formation with good clinical outcome.

KEYWORDS

Pramipexole, Osteogenesis, Callus Formation, Perimenopausal Females

INTRODUCTION

How the nervous system regulates bone remodeling is an exciting area of emerging research in bone biology. Mounting evidence in the field is beginning to suggest that inputs meditated through neurotransmitters directly affect osteoclasts.

We conducted a pilot study over a period of 3 months to observe the clinical effects of Pramipexole, particularly on callus formation in distal radial fractures as observed through USG scans in human females in the age group of 40 to 60 years.

DOPAMINE AND ITS PHYSIOLOGY

Dopamine physiology introduction

Dopamine is a neurotransmitter that can be released by hypothalamic neurons to regulate bone metabolism through the hypothalamic-pituitary-gonadal axis.

The dopamine transporter (DAT) is believed to control the temporal and spatial activity of released DA by rapid uptake of the neurotransmitter into presynaptic terminals.

Dopamine receptor pharmacology

Dopamine has been studied over a long period of time and has been found to have 5 receptors expressed in the body, D1 to D5, all of which are G protein-coupled receptors which primarily have cAMP mediated signaling processes, but have recently been also found to have alternative G protein coupling or G protein-dependent mechanisms via ion channels (Beaulieu & Gainetdinov, 2011).

Dopamine and calcium and phosphorus metabolism

Dopamine has long been suspected to have a hand in the calcium and phosphorus metabolic pathways, due to the increased risk that parkinsonism disease (PD) patients have for osteoporosis, with overall significantly lower Bone Mass Density observed among PD patients as compared to healthy controls suggesting that dopamine, through endocrine alterations in the hypothalamic-pituitary-gonadal axis such as reduced plasma levels of growth hormone or ACTH, acts as mentioned above. (Figueroa & Rosen, 2020).

DOPAMINE EFFECT ON OSTEOCLASTS

Dopamine receptor expression on osteoclasts

Dopamine receptors of all types have been found to be expressed on the surface of monogenic osteoclasts in humans, responding particularly to D2-receptor agonists such as pramipexole and quinpirole, through suppressed intracellular cAMP concentration and decreased expression of NFATc1 mRNA expression in osteoclast precursor cells both in human in-vitro cultures and murine ex-vivo samples (Hanami et al., 2013).

Dopamine – osteoclast pathway

Recently there has been some light shed on the pathway that is utilized in suppression of osteoclast differentiation by Dopamine through D2 receptor agonism with indications that it is via the cAMP/PKA/CREB pathway (Wang, Han, et al., 2021).

Utilization Of D2-Osteoclast Pathway In Achieving Clinical Outcomes In Orthopedic Cases

Dopamine coatings on titanium implants have shown promise to alter the efficacy of clinical outcome in orthopedic cases with examples such as dopamine-alginate coated titanium implants drastically improving the level of inhibition of RANKL-induced osteoclastogenesis as well as enhancing adhesion and differentiation of precursor cells (Wang, Wang, et al., 2021).

Titanium implants in-vivo tend to induce a state of chronic inflammation in the body with increased expression of osteoclasteo genesis. Murine models with titanium micro particles implanted in-vivo showed that there was decreased formation of this state in the simultaneous presence of dopamine in a dose-dependent manner with significant decrease in absolute count of osteoclasts as compared to models without presence of dopamine, with an interesting reversal seen when D2-receptor antagonist haloperidol was administered (Yang et al., 2016).

PRAMIPEXOLE PHARMACOLOGY

Pramipexole pharmacology proper

Pramipexole is a clinically effective non-ergot dopamine agonist with high selectivity for interacting with dopamine D2 subfamily receptors (D2, D3, and D4 receptor subtypes) and has little interaction with adrenergic or serotonergic receptors (Dooley & Markham, 1998).

Pramipexole has been used as monotherapy in PD or as adjunctive therapy to levodopa with progressing studies showing statistically and clinically significant effects on patients with early PD disease (Hubble

et al., 1995).

Pramipexole has also been shown to have multiple applications in psychiatry emerging as a new treatment modality for treatment-resistant bipolar and unipolar depression. Indeed, it is noted to be among a handful of drugs that have shown efficacy for treating bipolar depression as well as unipolar depression and depression associated with PD, with controlled trials also supporting its use in restless-legs syndrome and in fibromyalgia (Aiken, 2007).

Pramipexole and Restless Legs Syndrome

There have been multiple studies that have investigated the effects of Pramipexole in Restless Legs Syndrome (RLS). Montplaisir et al. (1999) in a double-blind randomized trial with ten patients noted that Pramipexole was "the most potent therapeutic agent ever tested for RLS" (Montplaisir et al., 1999). Winkelman et al. (2006), in a double blinded randomized placebo-controlled 12-week trial observed the efficacy and safety of using Pramipexole in RLS and reported statistically and clinically significant advantages over placebo treatment with good tolerance and the most frequent adverse effects being only nausea and somnolence (Winkelman et al., 2006).

Fractures of the distal radius are the most frequent fractures encountered by orthopaedic trauma surgeons accounting for 17.5% of all adult fractures. In all studies the incidences in females are higher than males by a factor of two to three (Tornetta, 2015).

METHODOLOGY

A sample size of 12 perimenopausal (40-60 years of age) females was taken with the inclusion criteria being a distal radial fracture in the said group. No blinding was done and cases were randomly selected from presentation at outdoor. Cases were subsequently randomly allotted to either of two treatment arms: either only symptomatic treatment i.e. treatment with pantoprazole and paracetamol, or, symptomatic treatment with the addition of 0.5 mg of Pramipexole daily before sleep for a total of 4 weeks. Both arms included proper manipulation of limb and reduction of fracture followed by plaster cast immobilisation which was subsequently removed after 4 complete weeks. Ultrasonography of the distal end of affected radius was done following completion of treatment arms to obtain the clinical endpoint – volume of callus formation. Volume of callus formation was estimated through a cuboidal model composed of the maximal measurements obtained in three orthogonal planes through the callus.

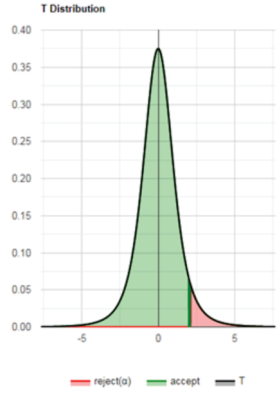

Figure 1: Graph showing the result's place within the T-distribution.

Source: www.statskingdom.com

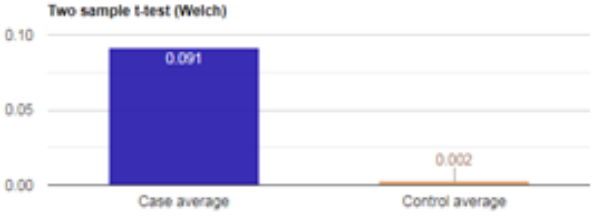

Figure 2: Graph showing the difference between the means of the two groups.

Source: www.statskingdom.com

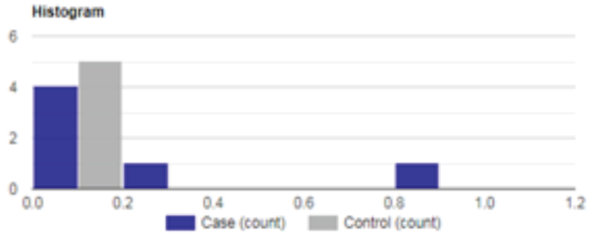

Figure 3: Graph showing the distribution among the groups and the case outlier is also visible, while the control outlier is within the rest due to differences of scale.

Source: www.statskingdom.com

RESULTS

The graph of the raw cases and their relation to the mean was plotted to observe for the presence of any outlier case (Tukey's Fences i.e. > 1.5 IQR away from Q1 or Q3 were used). 1 outlier case was found within both the controls and the cases and were subsequently cleaned out from the raw data as it might have introduced bias. Following this, the normality of the data was tested using the Shapiro-Wilk Test and both groups of cases were shown to be statistically significantly normally distributed ($p<0.05$).

A total of 11 cases and controls were studied. The mean callus volume of the cases after 4 weeks of treatment was 0.0913816 cm^3 (n=5) while in contrast the mean callus volume of the controls was 0.00243350 cm^3 (n=4).

The standard deviations of the two groups were widely different, making Welch's t-test a better test for the data as it does not assume equal standard deviations between the groups.

The Welch's t-test statistic was calculated for the two groups and resulted in a value of 2.045787 (DF=4.0085, right tailed) with a significance of $p = 0.055$ (just significant). The standardized effect size estimated from the data was found to be large (1.21).

DISCUSSION

Results in the light of past literature:

The study was from the outset designed as a pilot study with small sample size designed to probe the potential effect size that might be present using Pramipexole in this scenario. One individual from both the control and case arms proved to be an outlier as calculated by Tukey's Fences (k=1.5) and were subsequently identified and eliminated.

Although several emerging studies were focussing on in-vitro models and murine models over the last few years, there was no data on actual human interaction with the drug in the specified context. For that matter, there was also a serious dearth of data that might lead to an estimate of effect size that might be used in study planning.

Student's T test was not used as a fundamental assumption of the test is that the two groups being compared have equal SDs. This was found to be not so, and so, Welch's T test was used instead in an unpaired, right tailed configuration. It was highly expected from results of earlier studies, that the pramipexole group would out-perform the control group, and as such a right tailed t-test was applied in this case to better utilise low test power. This led to some rather interesting results: An effect size of 1.21 (High) was obtained, being just statistically significant ($p = 0.055 > 0.05$). It is arguable that with increased sample size that the p-value would definitely be lower than 0.05. This feeling is further strengthened by the value of the apriori power that the test achieved (0.1634) which is quite low and therefore indicates that the test might not reject an incorrect null hypothesis.

It is therefore reasonable to suggest that there is significant indication of a statistically significant large effect size lurking in these populations. Hence, it is highly recommended to undertake a full-fledged study with better sample size, and more informed pre-planning.

Drawbacks of the study:

One of the major drawbacks of this study is the small sample size which leads to decreased capability for predicting the effect size of Pramipexole. Another problem is that cuboidal estimates of an irregular three-dimensional callus make it harder to draw conclusions as there is significant room for improvement in accuracy of

measurement of volume which may shift the actual mean difference to a certain extent. Furthermore, progressive callus measurements were not taken, making it difficult to ascertain the dose-dependency relationship of Pramipexole in this scenario. In addition, the study was not blinded in any manner and more systematic randomisation might have led to further changes in results as a result of decreased inevitable bias. A significant part of this interpretation rests on the assumption that patient compliance is good as discharged outpatient department patients are not monitored directly for their compliance. Finally regional, ethnic and other factors may also play a role in the final result obtained and were not eliminated from the result through matched pair creation leading to potential uncertainty over the absolute contribution to the final effect size by Pramipexole alone.

Areas of future study:

Our study has several weak points as highlighted above that could have introduced significant bias into our results, and there is also the question of why two individuals became outliers in such a manner. Perhaps other factors which are unknown currently play a concurrent role in Pramipexole-augmented osteogenesis and should be controlled in future studies. A larger sample size with some blinding and some more randomisation in case selection would lead to a much more respectable result and it is hoped that it is not far off before that is achieved. In addition, the dose-effect-time relationship between Pramipexole and the osteogenesis in these cases should also be observed to enable dose titration, and further more the effect of pramipexole on callus formation in distal radial fractures should be compared to other fracture sites and fractures in men as well to observe for the impact of those factors on the overall osteogenesis process to make it more clinically relevant to consider prescribing this drug on a frequent basis during fracture healing.

CONCLUSIONS

There are practically no clinical studies that directly observe the effect of Pramipexole on callus formation in orthopaedic cases so far, although there is mounting evidence that suggests it could be useful clinically. Noting this we have tried to conduct a pilot study to gain an idea of how effective it might be, admittedly with potentially significant bias. We hope that our study can provide ground and perspective for future larger and more well controlled studies that can eventually establish the answer to the question much more firmly.

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