Combined Treatment with Oral Hypoglycemic Agents and Insulin in Longer Run May Lead to Cognitive Derangement Secondary to Hypoglycemia

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ABSTRACT

To determine the risk associated with combined therapy of oral hypoglycemic agents and insulin in the development of cognitive decline secondary to hypoglycemia. The study comprised of two arms, in arm 1 (n=30) diabetic patients on OHA and insulin combined therapy were observed for cognitive derangement based on Mini Cog score (Pearson's correlation r was calculated between the two) and the patients were also ruled out for hypoglycemia episodes. Similarly, in arm 2(n=30), only OHA therapy patients were evaluated on the same parameters using Pearson's correlation. Mean Mini Cog scores were found to be 1.79 in patients on combinational therapy of OHA and insulin. In the case of patients only on OHA for diabetes control mean Mini Cog, the score was 2.0. Pearson's coefficient r 1 between OHA plus insulin duration of therapy in years with Mini Cog score was -0.5831 at a statistically significant p value of 0.0007. While on the other hand, patients only on OHA therapy (in years) were not significantly correlated with Mini Cog scores.(r 2= - 0.0149 ; p value =0.93771).In the arm 1 (OHA + Insulin(n=30)), the average number of hypoglycemia episodes were found to be 2.633 as compared to the OHA only group in which mean hypoglycemia episodes were 0.866. There was a significant difference in the hypoglycemia episodes, as confirmed by the student t-test (4.06368) at a p value = 0.000147. Based on the study findings, combined Treatment with Oral Hypoglycemic agents and insulin in longer run may lead to cognitive derangement secondary to hypoglycemia.*Significance level <0.01, Negative correlations are indicative of lower the values of battery scores higher would be cognitive derangement.

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INTRODUCTION

Diabetes is one of the key disease burdens of the globe. Multiple studies have been conducted to find an association between diabetes and cognitive decline and dementia. Oral hypoglycemic agents are the backbone for managing type 2 Diabetes in an early phase (ICMR, 2018). Sulphonylureas are associated with hypoglycemia episodes (Klein-Schwartz *et al.*, 2016). In a metanalysis (Andersen and Christensen, 2016) did find adding more than one therapy to OHA may lead to hypoglycemia. In another study, it was found that adding insulin to met-

formin can have a higher risk of developing hypoglycemia (Roumie et al., 2016). Research suggests that the risk of hypoglycemia increases with age, duration of Diabetes and combinational therapy of OHA and Insulin (Amiel et al., 2008).

In a retrospective study conducted in Japan, multiple factors like age, cognitive decline, combinational therapy with of Insulin and sulphonylureas have been cited as risk factors for severe hypoglycemia (Ikeda et al., 2018).

In a study conducted by (Lin et al., 2018), about 66% of the patients on combination therapy of OHA and Insulin suffered with moderate hypoglycemia (Chin et al., 2016) investigated the association between hypoglycemia episodes and cognitive decline and did find that linear correlation between the two. In another study, it was found that in the case of severe hypoglycemia episodes, the risk of development of cognitive decline was much higher (Ryan et al., 2016). Another aspect to be kept in consideration with respect to the pathophysiology of cognitive decline is advanced glycemic end products (AGEs), which are produced secondary to uncontrolled long-duration diabetes (Gorska-Ciebiada et al., 2015). Brain insulin resistance has also been found correlated with cognitive decline in Diabetes (Arnold et al., 2018).

Cerebral microinfarcts also add to the pathophysiology of dementia in Diabetes type 2 (Biessels and Despa, 2018).

(Rasch and Born, 2013) explained the importance of sleep in memory consolidation. Others indicated REM sleep is more important for memory consolidation.

(Gupta et al., 2018) presented a correlation between different pathophysiologies involved in the cognitive derangement in Diabetes (Gupta, 2018) and role of sleep in memory consolidation and mechanism of cognitive decline in case of poor sleep or decreased sleep (Refer Figure 1).

In the current study, we hypothesized that combinational OHA and Insulin therapy has a higher risk of developing cognitive derangement as compared to OHA only group. We further hypothesized that higher cognitive decline in the OHA plus Insulin therapy group can be secondary to hypoglycemia as the combinational therapy had a higher incidence of hypoglycemia episodes.

MATERIALS AND METHODS

Patients were enrolled from either outpatient department or hospitalized patients from Sarvodaya Hospital and Research Center, Faridabad, Delhi NCR, India. Ethical clearance was sought from the University Ethics Committee of Amity University Uttar Pradesh, Noida, All the subjects have provided written informed consent to participate in the study.

The study comprised of two arms (refer Figure 6), in arm 1 (n=30) diabetic patients on OHA and insulin combined therapy were observed for cognitive derangement based on Mini Cog score (Pearson's correlation r was calculated between the two)and the patients were also ruled out for hypoglycemia episodes. Similarly, in arm 2(n=30), only OHA therapy patients were evaluated on the same parameters using Pearson's correlation. Demographics details can be referred to as per the Table 1. The current study was a single point prevalence study.

Inclusion and Exclusion criteria

Inclusion criteria

1. 35 –80 years of age

2. Type 2 DM patients as per "American Diabetic Association "

3. Greater than equal to 5 years of Diabetic History

4. Greater than 7 HBA1C

5. Willing to participate in the study and provide informed consent

Exclusion criteria

1. Age less than 35 years

2. Pregnant women and Children

3. Substance abuse

4. Significant Neurological, Psychiatric disease

Cognitive batteries

We used Mini Cog battery for cognitive assessment post getting written permission from

"The Alzheimer's Association" (http://www.alz.org).

Statistical analysis

We used IBM SPSS trial version for the statistical analysis. Mini Cog depicted the cognitive decline of the patients. To establish an association between Mini Cog and duration of OHA plus Insulin therapy in years, Pearson's correlation coefficient (r) was used. Similarly, Pearson's correlation coefficient (r) was

Table 1: Different variables along with the respective range

Variables	Range
Age (Years)	35-75
Weight (kg)	45-92
Duration of diabetes (Years)	6-17
No. of hypoglycemic episodes	0-9
HBA1C values	7-17

Table 2: OHA+Insulin therapy versus OHA treatment groups versus corresponding Pearson's coefficient

Treatment Group-Therapy duration in years	Mean Mini Cog Score	Pearson's Correlation	p value (<0.05)
OHA + Insulin(n=30)	1.79	-0.5831	0.0007*
OHA only (n=30)	2	-0.0149	0.93771**
*Significant	**Not Significant		

Table 3: OHA+Insulin therapy versus OHA treatment groups versus corresponding Hypoglycemia episodes in both arms

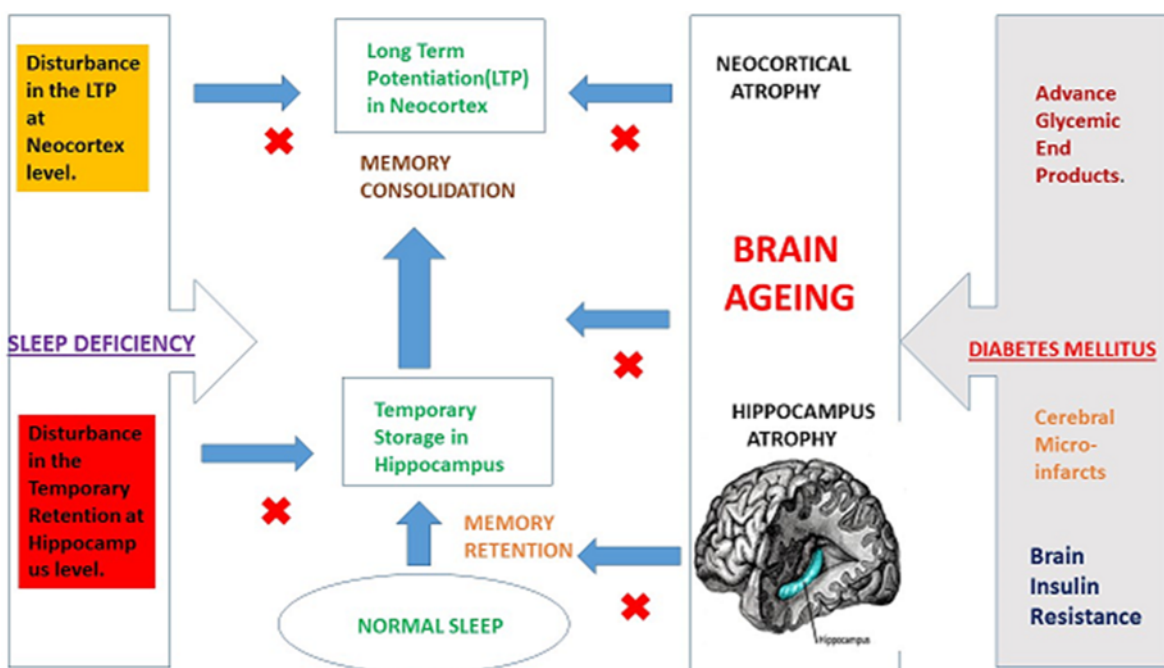| Treatment Group-Therapy duration in years	Mean number Hypoglycemia Episodes	t-test value	p value(<0.05)
OHA + Insulin(n=30)	2.633333333	4.06368	0.000147* *Significant

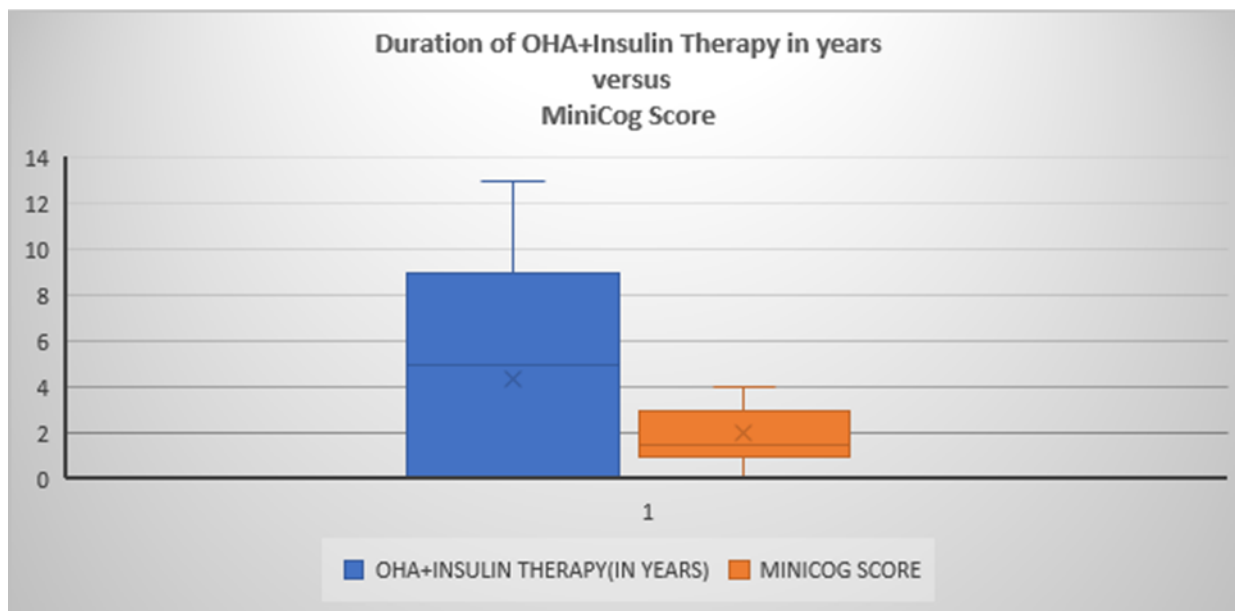**Figure 1: Proposed hypothesis**

Figure 2: Box and Whisker Plot -OHA +Insulin Therapy(years)versus Mini-Cog Score
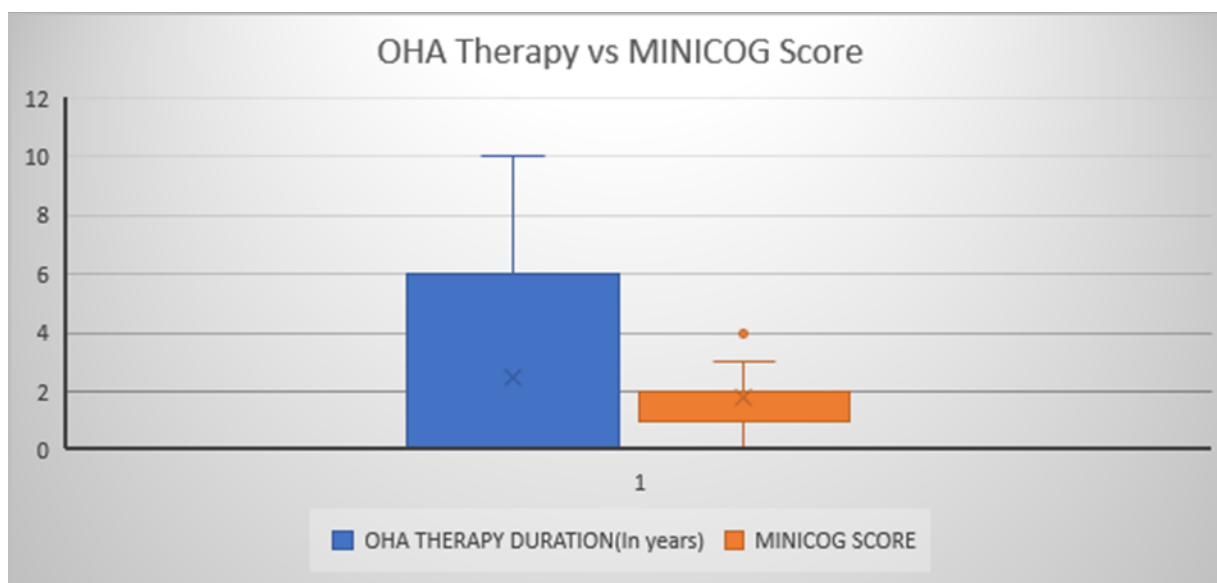

Figure 3: Box and Whisker Plot -only OHA Therapy (years)versus Mini-Cog Score

also calculated for the arm on only OHA therapy to find an association with Mini Cog scores.

Both the groups were also assessed for hypoglycemia episodes and the t-test was used to compare the results of both the arms at a p value less than 0.05 and 95% confidence interval.

RESULTS AND DISCUSSION

OHA and Insulin combinational therapy was associated with higher Cognitive derangement as compare to OHA only arm

Mean Mini Cog scores were found to be 1.79 in patients on combinational therapy of OHA and insulin. In the case of patients only on OHA for diabetes control, mean Mini- Cog score was 2.0. Pearson's coefficient r 1 between OHA plus insulin duration of therapy in years with Mini Cog score was - 0.5831 at a statistically significant p value of 0.0007. While on the other hand, patients only on OHA therapy (in years)were not significantly correlated with Mini Cog scores.(r 2= - 0.0149 ; p value =0.93771). Refer to Table 2 for details.

Higher Cognitive derangement in OHA and Insulin combinational therapy may be associated with hypoglycemia episodes in this arm

In the arm 1 (OHA + Insulin(n=30)), the average number of hypoglycemia episodes were found to
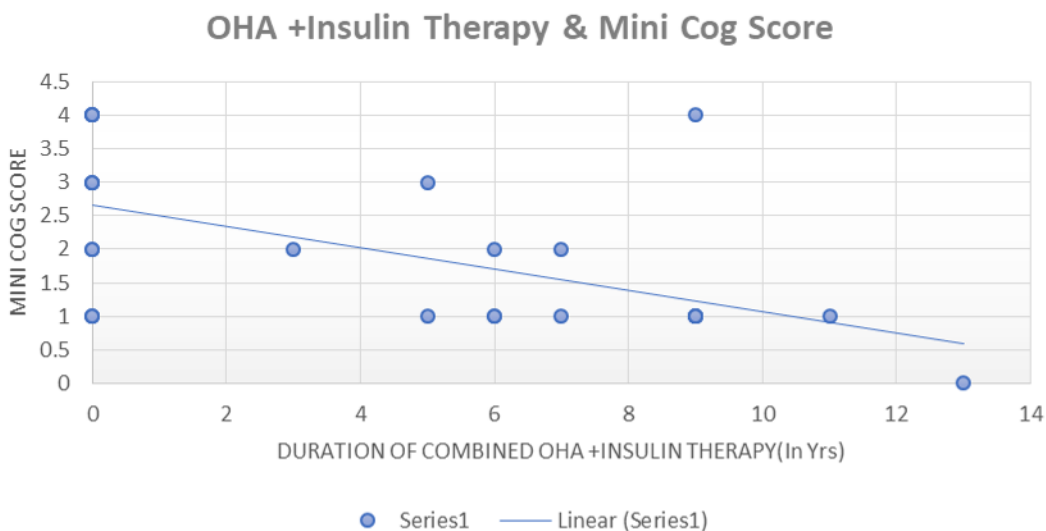
OHA +Insulin Therapy & Mini Cog Score

Figure 4: Scatter Plot -OHA +Insulin Therapy (years)versus Mini-Cog Score
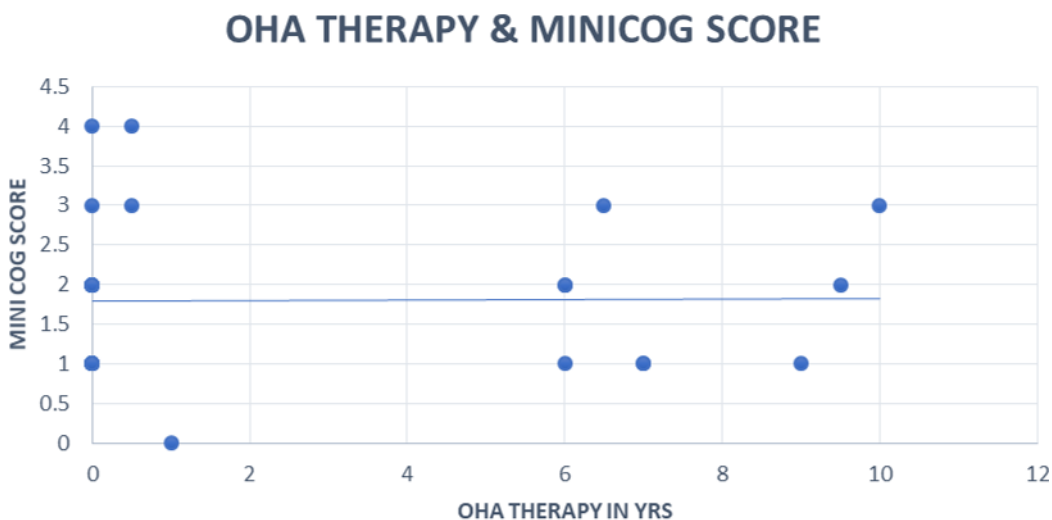
OHA THERAPY & MINICOG SCORE

Figure 5: Scatter Plot -only OHA Therapy (years)versus Mini-Cog Score

be 2.633 as compared to the OHA only group in which mean hypoglycemia episodes were 0.866. There was a significant difference in the hypoglycemia episodes, as confirmed by the student t-test (4.06368) at a p value = 0.000147. Refer to Table 3 for details.

Multiple studies have been conducted to find an association between Diabetes and cognitive derangement, which have been bringing forward concepts pertaining to the insulin resistance and dementia. memory impairment (Schrijvers *et al.*, 2010). Another group did find the relation between Alzhimer's disease and diabetes (Akter *et al.*, 2011). Researchers (Palta *et al.*, 2018) proposed its good to have diabetes in control to reduce the risk of cognitive decline. Animal models have also been successful to build up relationship between diabetes and dementia (Chomova *et al.*, 2017).

In the current study, we hypothesized that combinational OHA and Insulin therapy has a higher risk of developing cognitive derangement as compared to OHA only group. We further hypothesized that higher cognitive decline in the OHA plus Insulin therapy group can be secondary to hypoglycemia as the combinational therapy had a higher incidence of hypoglycemia episodes.

Current study results revealed that mean Mini Cog scores to be 1.79 in patients on combinational therapy of OHA and insulin and the same was 2.0 for the OHA only arm. Pearson's coefficient r 1 between OHA plus insulin duration of therapy in years with Mini Cog score was -0.5831 at a statistically significant p value of 0.0007. While on the other hand, patients only on OHA therapy (in years)were not significantly correlated with Mini Cog scores.(r 2= - 0.0149 ; p value =0.93771).Figure 2 depicts Box and Whisker Plot -only OHA plus
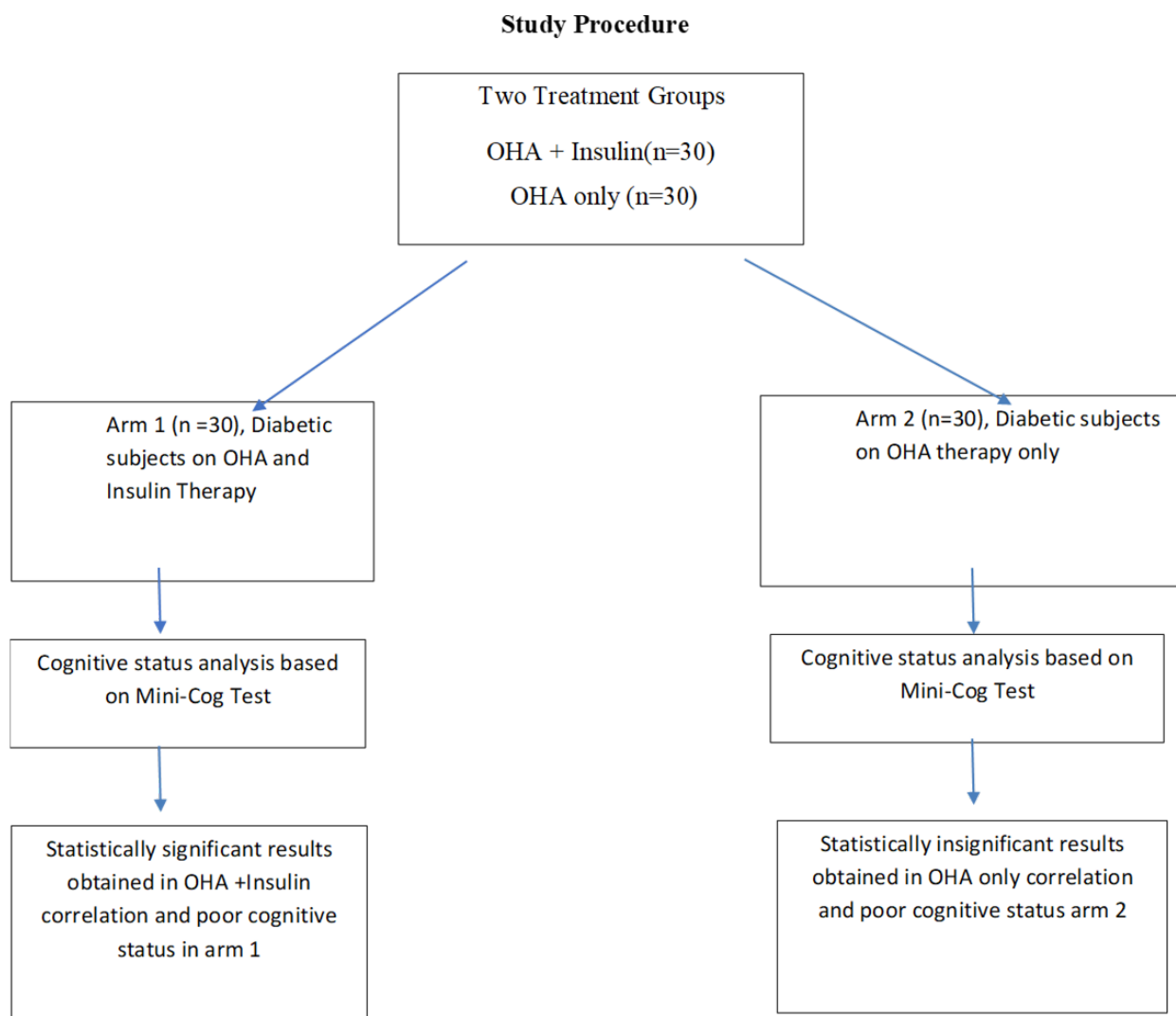
Study Procedure

Figure 6: Describesthe study pattern and distribution between the two arms

Insulin Therapy (years)versus Mini-Cog Score and Figure 3 indicate Box and Whisker Plot -only OHA Therapy (years)versus Mini-Cog Score.

With reference to Figure 4 Scatter Plot -OHA plus Insulin Therapy (years)versus Mini-Cog Score and Figure 5 depicts Scatter Plot -only OHA Therapy (years)versus Mini-Cog Score.

We can mark the difference in the presentation in both the cases. These results are in line with earlier studies, which Research suggests that the risk of hypoglycemia increases with age, duration of Diabetes and combinational therapy of OHA and Insulin (Amiel et al., 2008).

With respect to hypoglycemia episodes, in the arm 1 (OHA + Insulin(n=30)), the average number of hypoglycemia episodes were found to be 2.633 as compared to the OHA only group in which mean hypoglycemia episodes were 0.866. There was a significant difference in the hypoglycemia episodes, as confirmed by the student t-test (4.06368) at a p

value = 0.000147. These results are also aligned with previous studies like a retrospective study conducted in Japan, which indicated multiple factors like age, cognitive decline, combinational therapy with of Insulin and Sulphonylureas have been cited as risk factors for severe hypoglycemia (Ikeda et al., 2018).

Different studies have provided evidence of cognitive decline secondary to hypoglycemia episodes. (Chin et al., 2016) investigated the association between hypoglycemia episodes and cognitive decline and did find that linear correlation between the two. In another study, it was found that in the case of severe hypoglycemia episodes, the risk of development of cognitive decline was much higher (Ryan et al., 2016).

CONCLUSIONS

The current study provides significant findings related to the optimal usage of drugs for the man-

agement of type 2 diabetes by virtue of its results. To our knowledge, no other similar study has been conducted in north India. Cognitive assessment was based on the Mini-Cog battery, which has already been validated.

We compared two arms of the study: OHA plus insulin therapy and only OHA treatment based on the correlation of individual arms with Mini Cog scores. We further evaluated, an association of these two categories of patients with a probability of hypoglycemia episodes and their significance levels. Based on the study findings, combined Treatment with Oral Hypoglycemic agents and insulin in the longer run may lead to cognitive derangement secondary to hypoglycemia.

We studied multiple aspects related to cognitive decline and diabetes. Uncontrolled Diabetes has been associated with cognitive derangement and so is hypoglycemia episodes. OHA and Insulin therapy, in combination, has a higher risk of hypoglycemia episodes, later, in turn, can increase the probability of cognitive decline.

Combinational therapy with OHA and insulin can be necessary to manage the poorly controlled diabetes. Hence, it is very important to keep track of the treatment strategy while managing uncontrolled diabetes. Further, large scale studies are required to further validate the concept. Randomized double-blind placebo-controlled clinical trials can provide further support to current evidence.

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