ISSN- 0301-1216
Indian J. Prev. Soc. Med. Vol. 53, No.3, 2022

ORIGINAL ARTICLE

Use of CDR-sob and ADAS-cog score to check protective role of Non-steroidal Anti-Inflammatory Drugs in Alzheimer Disease: A Systematic Review and Meta-Analysis

Shashank Tripathi[1], Akash Asthana[2], Rachna Agarwal[3]

ABSTRACT

Background Alzheimer's disease is the major neurodegenerative disease, affecting more than two third cases of dementia in the world. NSAIDs are widely used anti-inflammatory analgesic agents representing 7.7% of worldwide prescription of which 90% are in patients over 65 year old. Based on mixed findings by different RCTs, a systematic review and meta-analysis on CDR-sob and ADAS-cog score was conducted to develop the better understanding on the protective role of Non-steroidal anti inflammatory drugs (NSAIDs) in AD. **Methods** Data base search was Pubmed, WebScience and Embase. RCTs investigating the effect of NSAIDs on AD or test scores assessing cognitive function in people without AD at baseline were included. Two indicators ADAS-cog score, and CDR-sob are used. Total 09 studies are included in the present Meta-analysis. **Results** For ADAS-score pooled the pooled summary effect size was calculated using random effect model was -0.03 with 95% C.I -0.13 to 0.07, which was statistically insignificant (p-value =0.44). For CDR-sob score difference, the pooled the pooled summary effect size was calculated using random effect model was -0.09 with 95% C.I -0.29 to 0.11 which was statistically insignificant (p=0.3812).For CDR-sob score, the pooled summary effect size was calculated using random effect model was 0.21 with 95% C.I -0.09 to 0.51, which was statistically insignificant (p-value = 0.1741). **Conclusion** Present Meta analysis shows that NSAIDs in general are not effective in treatment of AD. They also have no protective effect against development of AD on their sustained use.

Keywords: NSAIDS, Alzheimer's disease, Meta analysis

Introduction

Alzheimer's disease (AD) is the major neurodegenerative disease affecting geriatric population, affecting more than two third cases of dementia in the world[1]. Burden of Alzheimer's disease and related dementias in 2014 was 5 million in 2015 which has been projected to be more than 13.9 million by 2060.[2] It along with other dementias is major global health challenge, which may lead to high cost of health.[3-5] Multifactors like age, environment and genetic factors, along with accumulation of senile plaques and neurofibrillary tangles[6] are responsible for the pathogenesis of AD. Either all factors initiate the pathogenic cascade together or one leads to disease onset and the subsequent factors are involved in disease progression[7].

---

1. Research Scholar, Department of Statistics, Lucknow University, Babuganj, Hasanganj, Lucknow, Uttar Pradesh 226007; Email Id – tshashank70@yahoo.in; ORCID Id- https://orcid.org/0000-0001-7339-108)
2. Assistant Professor, Department of Statistics, Lucknow University, Babuganj, Hasanganj, Lucknow, Uttar Pradesh 226007.Email – akash020184@gmail.com ; ORCID Id- https://orcid.org/0000-0002-9509-9204).
3. Additional professor, Department of Neurochemistry, Institute of Human Behvaiour and allied Sciences, Delhi-110095; Email Id – rachna1000@hotmail.com; ORCID Id – https://orcid.org/0000-0003-2604-9809

Corresponding Author: Dr. Akash Asthana (Assistant Professor, Department of Statistics, Lucknow University, Babuganj, Hasanganj, Lucknow, Uttar Pradesh 226007; Email Id – akash020184@gmail.com

Postal – 442/480, Maheshpuri Colony, near Angira Hospital, Generailganj, Balaganj, Lucknow- 226003

Submission	27.06.2022	Revision	05.07.2022	Accepted	22.07.2022	Printing	29.09.2022

Prior Publication*: Nil*; Source of Funding:* Nil; *Conflicts of Interest*: None , *Article # 476

As per neuro-inflammatory theory proposed for pathogenesis of AD, inflammation of the microglia appears before brain damage [8,9]. Same has been reported in literature based on the study of the brain of patients with AD. These studies have shown chronically activated microglia and increased expression of the cyclo-oxygenase- 2 enzymes in neurotic plaques and tangles. [10,11]

Non steroidal anti inflammatory drugs (NSAIDs) are widely used anti-inflammatory analgesic agents representing 7.7% of worldwide prescription of which 90% are in patients over 65 year old[12]. In the United States, there has been a 40% increase in over-the counter NSAID use between 2005 and 2010 of which 26% report using more than the recommended dose[13-15]. Several epidemiological studies have reported protective role of NSAIDs against AD on its prolonged use in low doses by slowing down of cognitive decline especially in patients with mild to moderate AD(16)[16]. NSAIDs inhibit COX-2, which is upregulated in neurons leading to neuro-degeneration in AD[16]. In addition to it, studies show that small number of NSAIDs like ibuprofen, sulindac acid and indomethacin have ant amyloidogenic activity in vivo, function which is independent of COX inhibition[17, 18]. Alzheimer Disease Assessment Scale-cognitive Subscale and Clinical Dementia Rating Scale- sum of boxes are two scales, by which level of cognition may be measured in patients with Alzheimer disease.

In literature, studies show contradictory observations. Aisen et al 2002[1] suggested that NSAID may be useful in treatment of AD whereas, Reines et al 2004[8] found no significant role of NSAIDs in progression of AD. Hence a systematic review and meta-analysis need to be conducted for generating the promising evidence and to develop the better understanding on the protective role of NSAIDs in AD.

Material and Methods

1. ***Design*:** This systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis and followed a prior defined but unpublished protocol(19)
2. ***Protocol Registration:*** Our protocol has been registered on PROSPERO. Registration number is [**CRD42022301179**]
3. ***Data source and Literature*:** Two investigators (ST & AA) independently searched three databases PubMed, WebScience and MEDLINE from 1st January 2000 to 31st December 2021, with no language restriction. Studies published in other language then English, were included if their English translation is available. Also authors of studies other than English language were contacted to provide their English translation.

   To evaluate the use if NSAIDs as treatment for AD in subjects with proven or probable AD, the test scores assessing cognitive function in people without AD at baseline were included.

   Keywords used for searching literatures in above mentioned database where "RCT", "Alzheimer Disease", "AD", "NSAIDs", "NSAID", "Ibuprofen", "Rofecoxib", "Celecoxib", "Aspirin", "Naproxen" , "Nimesulide" , "Tarenflurbil" and "Indomethacin" or more of combination of these terms.
4. **Indicators used in Meta-Analysis:** There are total two indicators used in Meta-analysis from Experimental study design to assess the affect of NSAIDs on AD.

   4.1 ***AD Assessment Scale-cognitive Subscale*** **(ADAS-COG):** This scale focused on AD subject's cognition that includes 11 items to assess memory, understanding, temporal and spatial orientation and spontaneous speech. 00 to 70 is total score range, with higher scores indicating worst cognitive function [20].

   The respective scale was developed in 1980s, with AIM of assessing level of cognitive dysfunction in AD. This scale is Gold standard for assessing the efficacy of anti-dementia treatments. Pre-dementia

studies, ADAS-cog are often development was for use in studies in dementia where there is severe cognitive impairment[20].

4.2. ***Clinical Dementia Rating Scale- sum of boxes (CDR-sob):*** CDR-sob is useful score to stage AD severity with global assessment measures. This score help in management, communication and rapid selection of treatments which is approved for different stage of AD.

Compared with Washington University Clinical Dementia Scale (CDR), CDR-sob considers more detail quantities general Index and more information are provided in subjects with mild-to-moderate dementia. CDR-sob score combines both scores in single score.

Memory, Orientation, Judgement and problem solving, hobbies and personal care are 06 items included in score. Each domain is rated on 5-point scale from 0(normal) to 3(severe dementia), so that final result varies from 0 to 18.[21]

5 Study Selection

The eligibility criteria for including study in present Meta-analysis were as follows:-

- Studies conducted on population of age 55 years and above.
- Experimental Trials/Randomized Clinical Trials, to evaluate use of NSAIDs as treatment for AD in subjects with Alzheimer's.
- Studies reporting ADAS-cog and CDR-sob scores.
- Studies using diagnostic criteria NINDS-AIRDEN for outcome of AD and describe exposure to NSAIDs.
- Paper published in English Language only.
- Studies published from 2000 to 2021.

Studies were Excluded if:-

- They were not conducted in humans, used non-placebo group
- If mean difference or mean score of ADAS-cog and CDR-sob was not provided in study
- The studies not published in English and also its translation is unavailable.

6 Data Extraction

Two investigators (ST & AA) extracted data from the articles in standard file & third independent investigator (RA) validated data extraction. Data collected from each paper are shown in table 1 were as follows: - the study subjects characteristics (number of groups and number of participants in each group); the subjects characteristics (subject type, age, range); the experimental treatment (type of treatment, active ingredients, dose, frequency of dose and duration of treatment); the results (mainly quantitative scores of different cognitive tests expressed as mean and SD between baseline and the last follow-up assessment).

If in studies summary statistics were reported as mean and Standard Error, the Standard Error was transformed into SD using formula SD= S.E.*√n.

7. Outcomes

The change between follow-up and baseline on test assessing cognition (ADAS-cog and CDR-sob) were determined for subjects without AD at baseline in taking NSAIDs and control group (placebo). For CDR-sob both mean difference score and average mean score was used separately.

8. Data Synthesis and Statistical Analysis

All analysis was done using R Studio. A meta-analysis to estimate the overall treatment effect of AD with NSAIDs relative to placebo was performed. Pooled Standardized mean differences across all NSAIDs (last evaluation at the end of follow-up minus baseline data) were computed using fixed effect model and Random effect model and also Pooled Hazard Ratio were also computed using same respective models.

When there was heterogeneity in effect size across all studies, Q-statistics was used to examine this heterogeneity, which follows chi-square distribution and I^2-statistics explains the degree of heterogeneity in effect size across all the studies[22]. Heterogeneity in Meta-analysis means effect sizes varies from study to study, therefore identifying this effect sizes and quantifying Heterogeneity is important point to be considered. On the basis of these two measures of heterogeneity (Q and I^2), the appropriate model (Fixed effect Model and Random effect Model) is chosen to generate pooled effect size. If degree of heterogeneity in effect size was significantly high (i.e. I^2>30%) Random effect model is used; otherwise fixed effect model is used[22]. As Q-statistic & P-value will provide only the presence/absence of heterogeneity but not degree of heterogeneity, the magnitude of heterogeneity in effect size across selected studies will be assessed by I^2 statistics[22].

Table -1: Characteristics of studies selected for meta-analysis after rigorous systematic review from mentioned database

Study code	Author name & study (year)	No. of female		Age (SD)	Treatment	Dose (mg)	Frequency (dose/day)	Duration
		No.	%	Mean ± SD				
1.	Aisen et al (2002)	19	47.4	74±8.7	Placebo		2	84
		21	38.1	73± 9.1	Nimesulide	100	2	84
2.	Aisen et al (2003)	111	55.9	73.8± 8.0	Placebo		2	365
		118	48.3	74.1± 7.8	Naproxen	220	2	365
		122	54.9	73.7± 7.2	Rofecoxib	25	1	365
3.	Reines et al (2004)	346	52.0	75± 9	Placebo		1	365
		346	54.0	76± 8	Rofecoxib	25	1	365
4.	Thal et al (2005)	732	31.1	74.8± 6.0	Placebo		1	1460
		723	34.3	75.1± 6.0	Rofecoxib	25	1	1460
5.	Jong et al (2008)	19	76.0	72.2± 9	Placebo		1	365
		19	53.8	72.7± 6.9	Indomethacin	100	1	365
6.	Wilcock et al (2008)	46	41.0	75.6± 6.8	Placebo		2	365
		48	50.0	75.7± 7.6	Tarenflurbil	800	2	365
7.	Pasqualetti et al (2009)	66	65.0	74.0± 7.8	Placebo		2	365
		66	61.0	73.7± 7.3	Ibuprofen	400	2	365
8.	Babiloni et al (2009)	17	70.8	74± 6.5	Placebo		2	365
		18	78.2	75.6± 6.7	Ibuprofen	400	2	
9.	Green et al (2009)	809	52.5	74.7± 8.4	Placebo	800	2	540
		840	49.4	74.6± 8.5	Tarenflurbil		2	540

The I^2 statistic describes the percentage of variation across studies that are due to real heterogeneity rather than chance alone. The I^2 statistic is an intuitive and simple expression of the inconsistency of studies' results. Unlike Q statistic, it does not inherently depend upon the number of studies considered[22]. Therefore, I^2 statistic must be calculated along with 95% confidence interval while conducting any meta-analysis to explore the degree of heterogeneity in effect size across various selected studies.

Forest Plot was made to display the result of individual included studies along with their 95% Confidence Interval and pooled effect size with its 95% Confidence Interval is also displayed at the bottom of the graph[22].

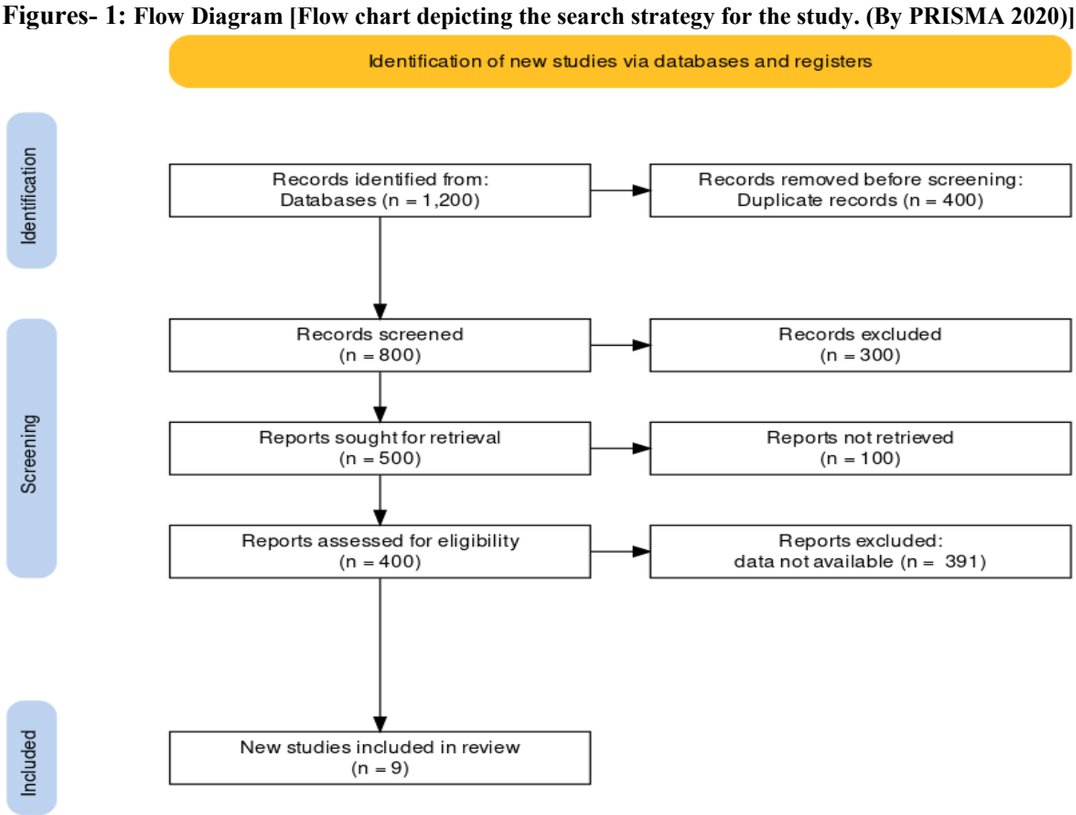
The Funnel plot, graphical method was made to check the Publication bias of studies was also constructed. The Funnel Plot is visual and informal method to examine the publication bias, but there are quantitative methods linear regression test, available to examine the existence of publication bias. Both analyses (Graphical & Quantitative) will be conducted in present study[22].

Result and Discussion

Characteristics of study

A total of 1200 relevant studies were identified during literature search on effect of NSAIDs for the treatment of AD. Out of 490 studies, initially 09 studies could be included for Meta analysis following inclusion criteria and rest 481 studies were excluded (Figure 1).

Figures- 1: Flow Diagram [Flow chart depicting the search strategy for the study. (By PRISMA 2020)]



09 studies finally taken for the present Meta analysis, in which the NSAIDs used, were Ibuprofen, Indomethacin, Tarenflurbil, Aspirin, Rofecoxib, Naproxen and Celecoxib. Among 09 studies, Meta analysis was performed based on ADAS-cog, CDR-sob score and CDR-sob mean difference. The study characteristics of these studies are summarised in Table 1. 09 studies included in the Meta analysis had representation from 4495 subjects, out of which 2164 were treated with NSAIDs and 2330 with placebo.

For ADAS-cog score, 01 study (Aisen et al 2002[1] used 02 drugs, therefore number of studies used for Meta-analysis of ADAS-cog score was 07. For CDR-sob average score, total 02 studies were used for Meta-analysis of this respective score. For CDR-sob score difference, 01 (Aisen et al 2003)[16] study used 02 drugs therefore total number of studies in Meta-analysis becomes 06 for this particular score.

Result of Meta-Analysis

ADAS-cog Score

Meta-analysis was performed on 07 studies with 2331 number of observations. Heterogeneity across 07 studies in effect size was not statistically insignificant. (Q-value = 5.88, p-value= 0.4365), but degree of heterogeneity was I^2=0.0% with 95% C.I 0.0% to 70.8%. Therefore, Random-effect-model was used to summarize the ADAS-cog score. **Figure 2(a)** displays the forest plot of meta-analysis for ADAS-cog score. 03 studies (Pasqualetti et al (2009)[23], Wilcock et al (2008)[24], Green et al (2009)[25] shown positive SMD 0.00 (-0.34, 0.34), 0.11 (-0.24, 0.46), 0.02 (-0.08, 0.12). Whereas, 04 studies (Aisen et al (2002)[1], Aisen et al (2003)[16], Jong et al (2008)[26] shown negative SMD -0.45(-1.08, 0.18), -0.01 (-0.27, 0.25), -0.24(-0.50, 0.02) ,-0.17(-0.80, 0.47). The pooled effect size was -0.03 with 95% C.I -0.13 to 0.07, which was statistically insignificant (p= 0.44). Green et al 2009[25] was assigned highest weight (54.7%), whereas Jong et al (2008)[26] was assigned lowest weight (2.3%) due to small sample size.

Figure-2: Statistical comparison of changes in (a) mean difference between pre- vs. Post treatment in ADAS-cog score (b) mean difference pre- vs. post-treatment (c) average mean score pre vs. post treatment in CDR-sob in Alzheimer's disease with their respective 95% C.I .

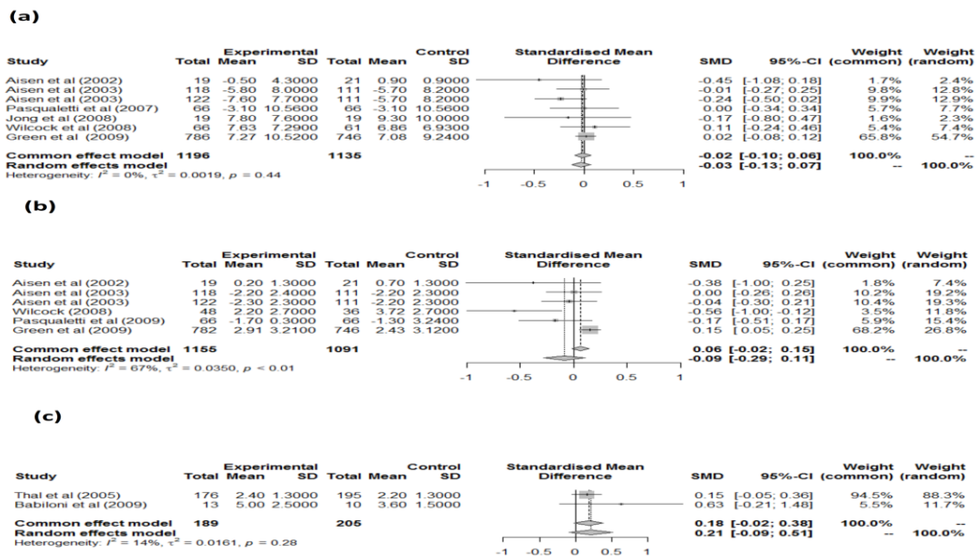
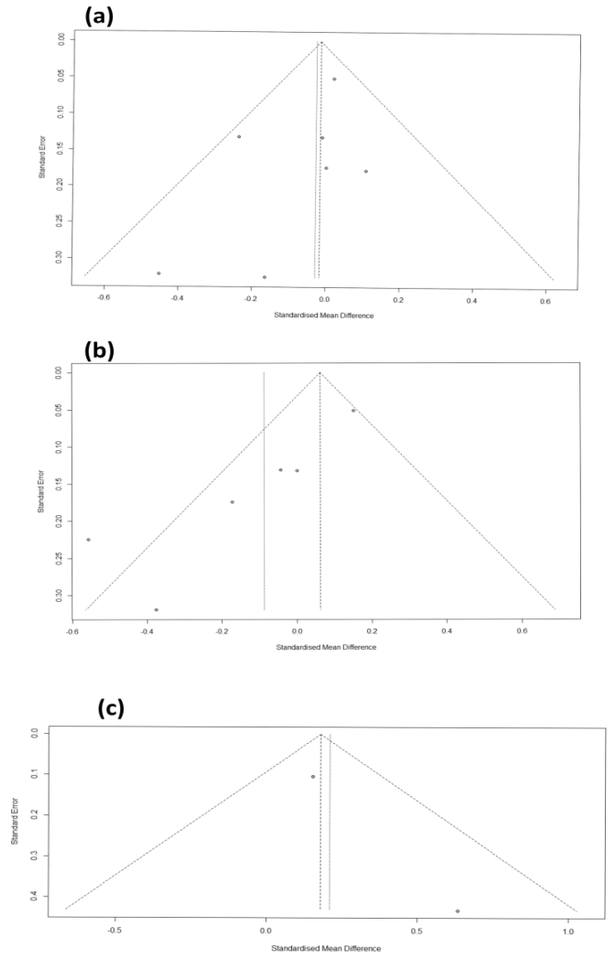


Figure- 3: Graphical method to check the publication bias (funnel plot) for studies reporting (a) mean difference in ADAS-cog score, (b) mean difference in CDR-sob score and (c) mean score in CDR-sob.



Funnel plot **[Figure 3 (a)]** shows no study out of inverted funnel, therefore no publication Bias was observed. Liner regression test shows statistically insignificant result of publication bias (p = 0.2144).

CDR-sob score difference

Meta-analysis was performed on 06 studies with 2246 number of observations. Heterogeneity across 06 studies in effect size was statistically significant. (Q-value = 15.21, p-value= 0.0095). Degree of Heterogeneity was I^2 = 67.1% with 95% C.I 21.8% to 86.2%. Therefore Random-effect-model was used to summarize result of CDR-sob score difference. **Figure 2(b)** displays the result of meta-analysis for CDR-sob score difference. 02 studies (Aisen et al (2003)[16], Green et al (2009)[25]) shown positive SMD 0.00 (-0.26, 0.26), 0.15(0.05, 0.25)], whereas 04 studies (Aisen et al (2002)[1], Aisen et al (2003)[16], Wilcock et al (2008)[24], Pasqualetti et al (2009) [23] shows negative SMD -0.38(-1.00, 0.25), -0.04 (-0.30, 0.21), -0.56 (-1.00, 0.12), -0.17(-0.51, 0.17). The pooled effect size was -0.09 with its 95% C.I -0.29 to 0.11

which was statistically not significant (p=0.38). Aisen et al 2002[1] was assigned the lowest weight (7.7%), whereas Green et al (2009) [25] assigned the highest weight (26.8%).

Funnel plot [Figure 3(b)] shows one study out of inverted funnel, therefore publication bias was present. Liner-regression test used, shown statistically significant result for publication bias (p-value =0.006).

CDR-sob average Score

Meta-analysis was performed on 02 studies with 394 observations. Heterogeneity across 02 studies in effect size was statistically insignificant (Q-value = 1.16, p-value=0.28). Degree of heterogeneity was I^2= 14.0% with no C.I. Therefore both Fixed-effect-model and Random-effect-model was used to summarise result of CDR-sob score. Figure 2(c) displays the forest plot of meta-analysis for CDR-sob average score. Both the studies (Thal et al (2005)[9], Babiloni et al (2009)[27]) shows positive SMD [0.15(-0.05, 0.36), 0.63(-0.21, 1.48)]. The pooled effect size using fixed effect model was 0.18 with 95% C.I -0.02 to 0.38, which was not statistically significant (p-value=0.07) and the pooled effect size using random-effect-model was 0.21 with 95% C.I -0.09 to 0.51, which was not statistically significant (p-value = 0.1741). In fixed-effect model lowest weight was assigned to study Babiloni et al 2009(27) (5.5%) whereas, highest weight was assigned to study Thal et al 2005 (94.5%)[9]. In random –effect model lowest weight was assigned to study Babiloni et al 2009[27] (11.7%) whereas, highest weight was assigned to study Thal et al 2005[9] (88.3%).

Funnel plot [Figure 3(c)] shows both studies inside inverted funnel, therefore no publication bias was present. Only 02 studies were involved, therefore no statistical test was used to check statistical significance of publication bias.

Discussion

Meta-Analysis findings of current study suggest that NSAID has shown no protective role in AD subjects using Standardized Mean difference of ADAS-cog, CDR-sob mean difference and CDR-sob mean score. Therefore such findings indicate there is no clinical improvement in subjects taking NSAIDs and subjects who are not exposed to NSAIDs. Funnel plot, created to check the publication bias, has shown no publication bias present in ADAS-cog and CDR-sob average score but publication bias was present in CDR-sob mean difference score. The liner regression test, a mathematical method, was also used to check publication which shows the publication bias exist in the studies for CDR-sob score difference, but statistically insignificant result was observed in case of ADAS-cog score. For CDR-sob average score, no test was used to check statistical significance of funnel plot, because only 2 studies were involved in analysis.

In present systematic review, no evidence was observed for protective effect of use of NSAID's on AD across 09 experimental studies, when given years before development of symptoms of AD. Usage of NSAIDs as protective effect in AD in present study to improve our understanding of role of NSAIDs in AD by making several conjectures are as follows, firstly, age of subjects taken in present Meta-Analysis, out of 09 studies all studies were done in diagnosed AD cases having more than 65 years of age. AD starts to occur over 20 years before cognitive decline with pathological changes. Szekely et al 2008[28] suggested reduced risk of AD in NSAIDs users was significant in younger age group. Hayden et al 2007[29] also reported use of NSAIDs before 65 years of age group had less cognitive decline as compared to individuals with more than 65 years of age group. Therefore it can be inferred that NSAIDs might show protective effect at early stage of AD but not effective in later stage of AD. It suggested performing RCT to study NSAIDs role as protective effect in AD after stratification of subjects by age. Secondly, Duration of Exposure to NSAIDs can be taken as second hypothesis similarly as age of subjects, NSAID exposure for long period of time cannot reverse outcome. As suggested by Szekely et al 2008[28] subjects with less age have less risk of AD, therefore it can be inferred that subjects who were exposed to NSAIDs for longer period have less risk of development of AD. As duration in 09 studies included varies from 84 days to 1716 days. Thirdly, Dosage of NSAIDs varies from 25 mg to 800 mg per day which could be

major factor which may affect therapeutic relevance of ϒ –secretase modulator effect in AD subjects[30]. Fourthly, Co-morbidities in AD subjects may be taken as one of important factor for such results, which modifies the protective effect[12]. Fifth, scores used in current Meta-Analysis like ADAS-cog and CDR-sob (both mean score and mean difference) are not only scores to measure cognitive decline in older person, there are n number of scores still available in clinical market to measure cognitive decline in older persons more than 60 year of age. Most of these scores used in study is for educated population and younger age group for accurate measure. Sixth, Apo lipoprotein E in AD subjects plays vital role in occurrence of disease[28]. Every individual with unique gene, therefore NSAIDs will react different for different individuals. APOE gene may alter the association between NSAID use and risk of developing AD. Study has found lower risk of AD only in NSAID use and risk of developing AD. Study has found lower risk of AD only in NSAIDs users with an AOOEϵ4 allele[28]. Seventh, Finally poor adherence to NSAIDs like aspirin and ibuprofen due to its severe gastrointestinal effects, leads to loss of subjects in follow up during these studies[12].

Subjects recruited in studies already have pathogenesis set in after microglia activation or they have recent NSAID exposure as shown by Rotterdam and Cache County observational studies[31,32]. These studies show no protection with NSAIDs used 2 years before onset of dementia. Subjects with healthier brain i.e. for those subjects whose onset of AD would be some years in the future exposed to NSAIDs may explain weak but non-significant protective effect of NSAIDs for AD as effect of NSAIDs exposure varies depending on stage of brain disease progression[30].

The present Meta-analysis neither shows that NSAIDs treatment decreases the progression of cognitive decline in AD nor any protective effect against development of AD on its sustained use. Scientific studies are not completed till their limitations are mentioned in clear language; therefore limitations of this study are as follows, first, Number of experimental study design taken for meta-analysis is few in number. Second, dosage in each included studies varies with huge margin. For inclusion of more number of studies, more studies are suggested to be done on subjects with less than 65 years age and are in long term use of NSAIDs. Third, no study included in present meta-analysis, assessed the effect of genetic factors like APOE genotype with on association of NSAID use and AD risk.

Strengths of our study are as follows Literature search strategy was rigorous, Research question was supported by clear eligibility criteria, Each step in review was done by multiple reviewers to ensure accuracy, Preferred Reporting items of Systematic Review and Meta Analysis during preparation of Manuscript is followed, Meta-Analysis was conducted adhering guidelines Cochrane Handbook of Systematic Review and Meta-analysis.

Conclusion

Non-steroidal anti-inflammatory drugs do not show any protective role in Alzheimer Disease subjects by using CDR-sob and ADAS-cog score.

Reference

1. Aisen PS, Schmeidler J, Pasinetti GM. Randomized pilot study of nimesulide treatment in Alzheimer's disease. Neurology. 2002 Apr 9;58(7):1050–4.
2. CDC Newsroom [Internet]. CDC. 2016 [cited 2022 Apr 1]. Available from: https://www.cdc. gov/ media/ releases/2018/p0920-alzheimers-burden-double-2060.htmo.
3. Prince M, Wimo A, Guerchet M, Ali GC, Wu YT, Prina M. World Alzheimer Report 2015. The Global Impact of Dementia. An Analysis of Prevalence, Incidence, Cost and Trends. 2015.
4. Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W, Ferri CP. The global prevalence of dementia: a systematic review and metaanalysis. Alzheimers Dement J Alzheimers Assoc. 2013 Jan;9(1):63-75.e2.

5. Wu YT, Beiser AS, Breteler MMB, Fratiglioni L, Helmer C, Hendrie HC, et al. The changing prevalence and incidence of dementia over time - current evidence. Nat Rev Neurol. 2017 Jun;13(6):327–39.
6. Miguel-Álvarez M, Santos-Lozano A, Sanchis-Gomar F, Fiuza-Luces C, Pareja-Galeano H, Garatachea N, et al. Non-Steroidal Anti-Inflammatory Drugs as a Treatment for Alzheimer's Disease: A Systematic Review and Meta-Analysis of Treatment Effect. Drugs Aging. 2015 Feb 3;3.
7. Talwar P, Sinha J, Grover S, Rawat C, Kushwaha S, Agarwal R, et al. Dissecting Complex and Multifactorial Nature of Alzheimer's Disease Pathogenesis: a Clinical, Genomic, and Systems Biology Perspective. Mol Neurobiol. 2016 Sep;53(7):4833–64.
8. Reines SA, Block GA, Morris JC, Liu G, Nessly ML, Lines CR, et al. Rofecoxib: no effect on Alzheimer's disease in a 1-year, randomized, blinded, controlled study. Neurology. 2004 Jan 13; 62 (1): 66–71.
9. Thal LJ, Ferris SH, Kirby L, Block GA, Lines CR, Yuen E, et al. A randomized, double-blind, study of rofecoxib in patients with mild cognitive impairment. Neuro-psychopharmacol Off Publ Am Coll Neuropsychopharmacol. 2005 Jun; 30 (6): 1204–15.
10. Cyclooxygeanase and Inflammation.
11. Cagnin A, Brooks DJ, Kennedy AM, Gunn RN, Myers R, Turkheimer FE, et al. In-vivo measurement of activated microglia in dementia. Lancet Lond Engl. 2001 Aug 11; 358 (9280) : 461–7.
12. Veronese N, Stubbs B, Maggi S, Thompson T, Schofield P, Muller C, et al. Low-Dose Aspirin Use and Cognitive Function in Older Age: A Systematic Review and Meta-analysis. J Am Geriatr Soc. 2017 Aug; 65 (8): 1763–8.
13. Scarpini E, Scheltens P, Feldman H. Treatment of Alzheimer's disease: current status and new perspectives. Lancet Neurol. 2003 Sep; 2 (9):539–47.
14. Etminan M, Gill S, Samii A. Effect of non-steroidal anti-inflammatory drugs on risk of Alzheimer's disease: systematic review and meta-analysis of observational studies. BMJ. 2003 Jul 19;327(7407):128.
15. Zhou Y, Boudreau DM, Freedman AN. Trends in the use of aspirin and nonsteroidal anti-inflammatory drugs in the general U.S. population. Pharmacoepidemiol Drug Saf. 2014 Jan; 23 (1) : 43–50.
16. Aisen PS, Schafer KA, Grundman M, Pfeiffer E, Sano M, Davis KL, et al. Effects of rofecoxib or naproxen vs. placebo on Alzheimer disease progression: a randomized controlled trial. JAMA. 2003 Jun 4; 289 (21): 2819–26.
17. McGeer PL, Schulzer M, McGeer EG. Arthritis and anti-inflammatory agents as possible protective factors for Alzheimer's disease: a review of 17 epidemiologic studies. Neurology. 1996 Aug; 47 (2):425–32.
18. Stewart WF, Kawas C, Corrada M, Metter EJ. Risk of Alzheimer's disease and duration of NSAID use. Neurology. 1997 Mar; 48(3): 626–32.
19. Hamrick I, Hafiz R, Cummings DM. Use of days of the week in a modified mini-mental state exam (M-MMSE) for detecting geriatric cognitive impairment. J Am Board Fam Med JABFM. 2013 Aug; 26 (4):429–35.
20. Kolibas E, Korinkova V, Novotny V, Vajdickova K, Hunakova D. ADAS-cog (Alzheimer's Disease Assessment Scale-cognitive subscale)--validation of the Slovak version. Bratisl Lek Listy. 2000;101(11):598–602.
21. O'Bryant SE, Waring SC, Cullum CM, Hall J, Lacritz L, Massman PJ, et al. Staging Dementia Using Clinical Dementia Rating Scale Sum of Boxes Scores. Arch Neurol. 2008 Aug;65(8):1091–5.
22. Introduction to Meta‐Analysis | Wiley Online Books [Internet]. [cited 2022 Apr 12]. Available from: https://onlinelibrary. wiley.com/doi/book/10.1002/9780470743386.
23. Pasqualetti P, Bonomini C, Dal Forno G, Paulon L, Sinforiani E, Marra C, et al. A randomized controlled study on effects of ibuprofen on cognitive progression of Alzheimer's disease. Aging Clin Exp Res. 2009 Apr;21(2):102–10.

24. Wilcock GK, Black SE, Hendrix SB, Zavitz KH, Swabb EA, Laughlin MA, et al. Efficacy and safety of tarenflurbil in mild to moderate Alzheimer's disease: a randomized phase II trial. Lancet Neurol. 2008 Jun;7 (6):483–93.

25. Green RC, Schneider LS, Amato DA, Beelen AP, Wilcock G, Swabb EA, et al. Effect of tarenflurbil on cognitive decline and activities of daily living in patients with mild Alzheimer disease: a randomized controlled trial. JAMA. 2009 Dec 16; 302 (23):2557–64.

26. de Jong D, Jansen R, Hoefnagels W, Jellesma-Eggenkamp M, Verbeek M, Borm G, et al. No effect of one-year treatment with Indomethacin on Alzheimer's disease progression: a randomized controlled trial. PloS One. 2008 Jan 23;3(1):e1475.

27. Babiloni C, Frisoni GB, Del Percio C, Zanetti O, Bonomini C, Cassetta E, et al. Ibuprofen treatment modifies cortical sources of EEG rhythms in mild Alzheimer's disease. Clin Neurophysiol Off J Int Fed Clin Neurophysiol. 2009 Apr; 120 (4): 709–18.

28. Szekely CA, Breitner JCS, Fitzpatrick AL, Rea TD, Psaty BM, Kuller LH, et al. NSAID use and dementia risk in the Cardiovascular Health Study: role of APOE and NSAID type. Neurology. 2008 Jan 1; 70 (1):17–24.

29. Hayden KM, Zandi PP, Khachaturian AS, Szekely CA, Fotuhi M, Norton MC, et al. Does NSAID use modify cognitive trajectories in the elderly? The Cache County study. Neurology. 2007 Jul 17; 69 (3):275–82.

30. ADAPT Research Group, Lyketsos CG, Breitner JCS, Green RC, Martin BK, Meinert C, et al. Naproxen and celecoxib do not prevent AD in early results from a randomized controlled trial. Neurology. 2007 May 22; 68(21):1800–8.

31. Szekely CA, Thorne JE, Zandi PP, Ek M, Messias E, Breitner JCS, et al. Nonsteroidal anti-inflammatory drugs for the prevention of Alzheimer's disease: a systematic review. Neuroepidemiology. 2004 Aug; 23 (4):159–69.

32. in t' Veld BA, Ruitenberg A, Hofman A, Launer LJ, van Duijn CM, Stijnen T, et al. Nonsteroidal anti inflammatory drugs and the risk of Alzheimer's disease. N Engl J Med. 2001 Nov 22; 345 (21):1515–21

Citation: Tripathi S., Asthana A, Agarwal R. Use of CDR-sob and ADAS-cog score to check protective role of Non-steroidal Anti-Inflammatory Drugs in Alzheimer Disease: A Systematic Review and Meta-Analysis. Indian J Prev Soc Med, 2022; 53 (3): 173-183.