Efficacy of Aidi Injection Combined With Radiotherapy for the Treatment of Nasopharyngeal Carcinoma: A Systematic Review and Meta-Analysis

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Abstract

Objective: Radiotherapy (RT) is the first choice in the treatment of nasopharyngeal carcinoma (NPC) but there are many adverse reactions. There is evidence that Aidi injection can improve the effect of RT and reduce the occurrence of adverse reactions after RT, but there is still a lack of evidence-based study. The objective of this study was to evaluate the efficacy and safety of Aidi injection combined with RT in the treatment of NPC.

Methods: The PubMed, Cochrane Library, CNKI, EMBASE, Web of Science, CBM, Wanfang, and VIP data were thoroughly searched for randomized controlled trials (RCTs) on Aidi injection combined with RT against NPC until February 2021. The literature was screened, extracted, and evaluated by 2 investigators independently. Meta-analysis was performed by RevMan5.3 and Stata 14.0, and the quality of evidence was evaluated by Grading of Recommendations Assessment, Development, and Evaluation (GRADE).

Results: In this study, we included 9 RCT studies involving 422 patients. The results showed significant between-group differences in complete remission rate (CRR) [relative risk (RR) = 1.17, 95% CI (1.04, 1.31), P = .009], Karnofsky Performance Status Scale (KPS) score [RR = 1.30, 95% CI (1.19, 1.42), P < .00001], leukopenia [RR = 0.65, 95% CI (0.54, 0.78), P < .00001], hemoglobin reduction [RR = 0.60, 95% CI (0.43, 0.84), P = .003], nausea and vomiting [RR = 0.60, 95% CI (0.45, 0.80), P = .0004], oropharyngeal mucosa injury (OMI) [RR = 0.25, 95% CI (0.15, 0.44), P < .00001], but the differences were not statistically significant in total effective rate (TER) [RR = 1.03, 95% CI (0.98, 1.08), P = .20 > .05], thrombocytopenia [RR = 0.78, 95% CI (0.52, 1.16), P = .22 > .05], and skin injury [RR = 0.81, 95% CI (0.64, 1.04), P = .1 > .05].

Conclusion: Aidi injection combined with RT can improve patients’ quality of life (KPS score) and reduce the adverse reactions caused by RT (such as leukopenia, hemoglobin reduction, OMI, nausea, and vomiting). However, limited by the quality and quantity of the included trials, more high-quality studies should be performed to verify our conclusions.

Keywords

Aidi injection, radiotherapy, nasopharyngeal carcinoma, cancer treatment, randomized controlled trials, meta-analysis

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Introduction

Nasopharyngeal carcinoma (NPC) is a malignant tumor originating from the epithelium of nasopharyngeal mucosa.1 It is characterized by hidden onset, deep lesions, and atypical early symptoms. Therefore, once diagnosed, the condition has been in the middle or advanced stage, and among some patients, tumor metastasis has appeared. Radiotherapy (RT), chemotherapy, and surgery are commonly used for the treatment of NPC. Since this is mostly squamous cell carcinoma, RT is considered as the first choice.2 However, the RT may damage important
organ and tissues around the nasopharynx and neck. This treatment often leads to adverse reactions, such as salivary gland injury, dry mouth, radioactive ophthalmic sequelae, mucositis, and hemotoxic reactions, which reduce the life quality of the patients. and even interrupts the treatment. In some patients whose lesions are under control, local recurrence or distant metastasis may appear later. 

At present, traditional Chinese medicine (TCM) has been extensively applied against cancers at all stages. It may improve the curative effect of chemoradiotherapy and reduce the occurrence of toxic side effects which has been proved clinically. Aidi injection (ZS2020236, China Food and Drug Administration) is an important TCM injection, which is widely used in the adjuvant therapy of malignant tumors in China. Table 1. As an anticancer TCM drug, Aidi injection is often used with chemoradiotherapy as an adjuvant therapy for lung cancer, liver cancer, stomach cancer, and so on. Aidi injection can reduce adverse reactions caused by tumor chemoradiotherapy, for example, gastrointestinal reactions and hepatorenal toxicity. It is safe, and may significantly improve patients’ life quality after chemoradiotherapy. Aidi injection is also being widely used in nasopharyngeal cancer.

A randomized controlled trial (RCT) reported that Aidi injection combined with RT could improve the life quality score and reduce toxic and side effects. There are more and more similar reports but it is difficult to draw a reliable conclusion from them for lack of systematic evaluation on the efficacy. This paper conducted a meta-analysis on RCTs of Aidi injection combined with RT against NPC so that relevant clinical work and scientific research may have reliable treatment protocols and an evidence-based basis.

### Methods

#### Study Registration

The paper was written under the guidance of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). See statement (Supplementary Table S1). The study protocol was registered at https://osf.io/j4uyh/ (DOI 10.17605/OSF.IO/J4UYH).

#### Eligibility Criteria

**Type of Studies.** We included all the RCTs only and excluded the reviews and other studies such as cohort, case–control, case series, and qualitative studies. The published abstracts were also excluded when unable to get the details.

**Types of Participants.** The diagnostic criteria refer to the diagnosis of NPC in Radiotherapy of Oncology. The patient was clearly diagnosed with NPC, whose diagnostic criteria were referred to Radiotherapy of Oncology. The international tumor-node-metastasis (TNM) system was used for tumor grading.

**Interventions.** Treatment group: Aidi injection combined with RT; control group: only the same RT as the treatment group.

**Types of Outcome Measures**

**Primary Outcomes.** Primary outcomes are as follows: (1) Karnofsky Performance Status Scale (KPS) and (2) total effective rate (TER). For evaluation criteria, refer to the WHO efficacy evaluation criteria: (i) Complete response (CR): Disappearance of all targeted lesions in two observations no less than 4 weeks interval; (ii) Partial response (PR): a >50% decrease in sum of products of the greatest diameters (SPD) of all lesions; without new lesions nor progression of any lesions; (iii) Stable disease (NC): a 50% decrease or 25% increase in SPD of one or more lesions; and (iv) Progressive disease (PD): a >25% increase over the smallest measurement in the single lesion, or the appearance of new lesions. TER = (CR + PR)/total number *100%.

**Secondary Outcome.** Secondary outcome indicators are as follows: Toxic and side effects (refer to Radiation Therapy Oncology Group [RTOG]): Criteria for the classification of acute radiation injury) including leukopenia, hemoglobin reduction, thrombocytopenia, ophthalmic sequela, mucosal injury (OMI), nausea, vomiting, and skin injury.

#### Exclusion Criteria

1. Repetitively published researches;
2. Studies of abstracts only or conference papers without available data;
3. Studies with noticeable errors or incomplete and unavailable data;
4. Studies with high bias risk.
5. Studies with other TCM therapies in treatment group such as acupuncture or other formula;
6. Studies without outcomes.

**Data Sources and Search Strategy**

The PubMed, Cochrane Library, CNKI, EMBASE, Web of Science, CBM, Wanfang, and VIP data were thoroughly searched from the database establishment to February 2021 with MeSH terms and free terms. Also, we searched for the potentially unpublished literature both in Google Scholar and Baidu. The words for search in English were Aidi, NPC, carcinoma, and nasopharyngeal, which in Chinese were Ai Di Zhu She Ye (Aidi injection), Bi Yan Ai (NPC), Bi Yan Lin Ai (nasopharyngeal squamous cell carcinoma). Supplementary Table S2 shows the search strategy in PubMed.

**Study Selection and Data Extraction**

The literature was independently screened by Renhong Wan and Anlan Zhao with the following procedures: (1) Remove the duplicated papers in EndNote X9. (2) Review titles and abstracts for preliminary selection. (3) Screen the full text in accordance with the criteria of inclusion and exclusion. Another investigator, Min Zhong, would resolve the discrepancies. The missing data or information was obtained by contacting the corresponding authors when necessary. All the following information was extracted into Microsoft Excel 2013: (1) General information of the first author, publication year, samples in each group, baseline information, tumor stage, and functional status score; (2) Interventions and course; (3) Outcome measures; and (4) Risk or bias assessment factors in RCTs.

**Bias Risk Assessment**

Bias risk assessment and results cross-check were performed by Renhong Wan and Anlan Zhao independently. Another investigator, Min Zhong, would resolve the discrepancies. The recommended tool for bias risk assessment in Cochrane Manual 5.1.0 was adopted.29

**Statistical Analysis and Data Synthesis**

The RevMan5.3 of Cochrane Collaboration was applied for meta-analysis. The weighted mean difference (WMD) was used for continuous variables if the measuring instruments and the units were consistent, otherwise standard mean difference (SMD) was used. Relative risk (RR) was used to analyze the dichotomous variables, and the 95% CI was provided for each effect size. Heterogeneity between the results was analyzed by the chi-square test, and quantitatively determined in combination with \( \hat{I}^2 \). \( \hat{I}^2 \geq 50\% \) indicated no significant heterogeneity between studies, and a fixed effect model (FEM) was used for the meta-analysis. \( \hat{I}^2 < 50\% \) indicated significant heterogeneity between studies. In this case, the sources of heterogeneity need be discussed by both subgroup analysis and sensitivity analysis. Only if significant clinical and methodological heterogeneity are excluded, a random effect model may be used for the meta-analysis. The sensitivity analysis was used for the influence of a single study on the combined effect size, as well as the stability of the meta-analysis results. Funnel plot would be used for publication bias for major outcome measures if \( \geq 10 \) researches were included, and potential publication bias would be evaluated by Egger’s and Begg’s tests.

**Results**

**Description of the Included Studies**

Preliminary screening obtained 83 relevant articles, and 38 remained after duplicate ones were removed. Through reading the titles and abstracts, 24 articles remained, and then, 15 of the 24 articles were excluded through full-text reading. At last, 9 articles were included.23,30–37 The screening procedure is shown in Figure 1. Table 2 shows the basic features of the included studies.

**Bias Risk Assessment**

The risk assessment tool by Cochrane Manual 5.1.0 was used to evaluate the quality of 9 included articles.23,30–37 One article used the method of random sequence generation correctly. None of the studies mentioned blinding. Combined with the intervention method, all the studies were evaluated as high risk; all studies were evaluated as low risk in the distribution of hidden, incomplete outcome indicators, selective report, etc. The results of bias risk assessment are shown in Figure 2.

**Outcome Measures**

**Primary Outcome Indicators**

**TER.** Eight RCTs were included,21,30–34,36,37 including 680 patients. Heterogeneity test: \( P = .13, \hat{I}^2 = 38\% \), without statistical heterogeneity. FEM results showed that for the TER, there existed no statistical difference between the 2 groups [\( RR = 1.03, 95\% CI (0.98, 1.08), P = .20 > .05 \)], (Figure 3). A subgroup analysis was performed according to the dosage of Aidi injection. The results showed that there was no heterogeneity for the three subgroups, and no statistically significant between-group difference (\( P > .05 \)) (Figure 4). In the Meta-analysis for separate re-evaluation on the complete remission rate (CRR), the No. of complete remission cases/total No. of cases \(*100\%\) was statistically heterogeneity: \( P = .68, \hat{I}^2 = 0\% \), without statistical heterogeneity. FEM meta-analysis results showed that the CRR of the 2 groups was [\( RR = 1.17, 95\% CI (1.04, 1.31), P = .009 \), with significant difference (Figure 5).

**KPS Score.** Six RCTs, including 504 patients,30–34,36 reported a KPS score. Heterogeneity test: \( P = .26, \hat{I}^2 = 23\% \), without statistical heterogeneity. The FEM results showed that for the KPS score, there was no statistically significant between-group difference [\( RR = 1.30, 95\% CI (1.19, 1.42), P < .00001 \)] (Figure 6). A subgroup analysis was performed according to the dose of Aidi injection. The results showed that all the 3 subgroups were
homogeneous. The FEM meta-analysis results were as follows: $[RR = 1.29, 95\% \text{ CI } (1.08, 1.55), P = .005]$; $[RR = 1.17, 95\% \text{ CI } (1.05, 1.30), P = .004]$; and $[RR = 1.56, 95\% \text{ CI } (1.25, 1.94), P < .00001]$. The difference was statistically significant (Figure 7).

Secondary Outcome Indicators

Leukopenia. Seven RCTs including 466 patients$^{23,30-35}$ reported leukopenia. Heterogeneity test: $P = .77$, $I^2 = 0\%$, without statistical heterogeneity. The results of FEM meta-analysis showed that for the leukopenia, there was statistically significant between-group difference $[RR = 0.65, 95\% \text{ CI } (0.54, 0.78), P < .00001]$ (Figure 8).

Thrombocytopenia. Three RCTs including 170 patients$^{30,34,35}$ reported thrombocytopenia. Heterogeneity test: $P = .46$, $I^2 = 0\%$, without statistical heterogeneity. The results of the FEM meta-analysis showed that for the thrombocytopenia, there was no statistically significant between-group difference $[RR = 0.78, 95\% \text{ CI } (0.52, 1.16), P = .22 > .05]$ (Figure 9).
Table 2. Basic Features of the Included Studies.

| Study cohort | No (T/C) | T     | C     | KPS Score | TNM staging | Course (days) | Dose of Adriamycin injection | Outcome |
|--------------|---------|-------|-------|-----------|-------------|----------------|-----------------------------|---------|
| Wang Q 2009  | 30/30   | -     | -     | ≥60       | I to IV     | 30 to 35       | 50 mL QD                   | ①③④    |
| Zhang HM 2010| 40/40   | -     | -     | ≥70       | II to IV    | 30             | 50 mL QD                   | ①②③④⑤ |
| Dong XR 2004 | 32/30   | 22/10 | 21/9  | ≥60       | II to III   | 49             | 50 mL QD                   | ①②③④⑤ |
| Chen S 2005  | 36/35   | 29/7  | 28/7  |           | II to IV    | 30             | 50 mL QD                   | ①②③④⑤ |
| Wang G 2003  | 22/20   | 17/5  | 16/4  | ≥60       | II to IV    | 28             | 50 mL QD                   | ①②③④⑤⑥⑦⑧|
| Wu ZX 2012   | 70/70   | 48/22 | 50/20 | >70       | II to IV    | 45             | 40 mL QD                   | ②       |
| Li JP 2010   | 50/50   | -     | -     | >60       | I to II     | 28             | 50 to 100 mL QD            | ①②     |
| Hu JZ 2013   | 60/56   | 46/14 | 43/13 |           | -           | >45            | 50 to 100 mL QD            | ②        |
| Zhang CJ 2005| 28/28   | 21/7  | 22/6  | 60-90     | I to IV     | -              | 50 to 100 mL QD            | ①②      |

Note: (1) TER; (2) Karnofsky Performance Status Scale; (3) Leukopenia; (4) OMI; (5) Nausea and vomiting; (6) Thrombocytopenia; (7) Hemoglobin reduction; (8) Skin injury.

Abbreviation: KPS, Karnofsky Performance Status Scale.
Hemoglobin Reduction. Three RCTs including 170 patients\textsuperscript{30,34,35} reported hemoglobin reduction. Heterogeneity test: $P = 0.98$, $I^2 = 0\%$, without statistical heterogeneity. The FEM results showed that for the hemoglobin reduction, there was statistically significant between-group difference [$\text{RR} = 0.60$, 95\% CI (0.43, 0.84), $P = .003$] (Figure 10).

Nausea and Vomiting. Five RCTs including 306 patients\textsuperscript{30–32,34,35} reported nausea and vomiting. Heterogeneity test: $P = .61$, $I^2 = 0\%$, without statistical heterogeneity. The FEM results showed that for nausea and vomiting, there was statistically significant difference between the 2 groups [$\text{RR} = 0.60$, 95\% CI (0.45, 0.80), $P = .0004$] (Figure 11).
Oropharyngeal Mucosal Injury. Five RCTs including 324 patients reported OMI. Heterogeneity test: $P = .76$, $I^2 = 0\%$, without statistical heterogeneity. The FEM meta-analysis results showed that for OMI, there was statistically significant difference between the 2 groups [$RR = 0.25$, 95% CI (0.15, 0.44), $P < .00001$] (Figure 12).

Skin Injury. Two RCTs including 123 patients reported skin injury. Heterogeneity test: $P = .97$, $I^2 = 0\%$, without statistical heterogeneity. The FEM meta-analysis results showed that for the skin injury, there was no statistically significant between-group difference [$RR = 0.81$, 95% CI (0.64, 1.04), $P = .1 > .05$] (Figure 13).

**Sensitivity Analysis**

The sensitivity analysis was carried out by a one-by-one elimination method, and effect size and $P$ value changes were observed after one-by-one elimination of included studies. The effect size of outcome indicators did not change significantly after excluding any article, indicating the results were reliable and stable.
Figure 8. Mate analysis for a comparison of leukopenia between groups.

Figure 9. Mate analysis for a comparison of thrombocytopenia between groups.

Figure 10. Mate analysis for a comparison of hemoglobin reduction between groups.

Figure 11. Mate analysis for a comparison of nausea and vomiting between groups.
Publication Bias

Considering that total 9 studies were included, we investigated the publication bias through Egger’s test and Begg’s test, and the results showed that there was no publication bias ($P = .1920 > .05$, $P = .1078 > .05$, respectively).

Evaluation of Quality of Evidence

Evidence quality was assessed by the Grading of Recommendations Assessment, Development, and Evaluation (GRADE). After being assessed by the GRADE evidence grading system, the KPS score, the degree of leukocyte, and hemoglobin reduction, the incidence of OMI, and the incidence of nausea and vomiting were all low, and the above outcome indicators all met the 2 downgrading criteria: (1) Risk of bias: Only one study accurately used the random method and none of the studies specifically described the allocation concealment and blinding. As it was an objective indicator, it was downgraded one level. (2) Imprecision: Downgrading was due to the small No. of included studies and wide confidence intervals (Table 3).

Discussion

The etiology of NPC is still unclear, but it is generally believed to be highly correlated with Epstein Barr (EB) virus, environmental factors, dietary habits, and genetic susceptibility. Traditional medicine assigned it to the categories of “sinusitis (Bi Yuan)”, “upper stony flat abscess (Shang Shi Ju)”, and “glanders (Bi Ju)”. According to the classification of TCM, the syndrome types of NPC can be divided into lung heat, blood stagnation, phlegm cagulation, and blood stagnation-phlegm coagulation. The TCM pathogenesis is deficiency in origin and excess in superficiality. Aidi injection is composed of cantharis (Mylabris phalerata Pallas), Radix Astragali (Astragalus membranaceus (Fisch.) Bge), ginseng (Panax ginseng C. A. Meyer), and acanthopanax root (Acanthopanax senticosus [Rupr. et Maxim.] Harms). Ginseng (Ren Shen) can greatly invigorate primordial qi, promote production of fluid, and benefit lung; Radix Astragali (Huang Qi) invigorates qi for consolidating superficialities and promotes pus discharge and tissue regeneration; Acanthopanax Root (Ci Wu Jia) can replenish qi and invigorate the spleen; Cantharis (Ban Mao) can remove blood stasis. All medicinal materials above are combined to treat both manifestation and root cause of the disease. Modern pharmacological studies have shown that Aidi injection has antitumor and immunomodulatory effects. The roles of active ingredients in it are as follows: ginsenoside can enhance the function of T and B cells, induce interferon and interleukin, and increase the activity of LAK and NK cells; astragalus polysaccharide can enhance reticuloendothelial phagocytosis, as well as the anticancer activity of T cells, NK cells, LAK cells, and IL-II. It can also enhance the ability to kill tumor cells; acanthopanax root (Ci Wu Jia) extract contains a variety of glycosides and acanthopanax polysaccharide, which can improve immunity, increase white blood cells, improve the adaptability of the body.
| Quality assessment | Summary of findings |
|--------------------|---------------------|
|                     | No. of patients | Effect | Relative (95% CI) | Absolute | Quality |
| No. of studies | Design | Limitations | Inconsistency | Indirectness | Imprecision | Other considerations | treatment | control | |
| New Outcome | | | | | | | | | |
| KPS score | Randomized trials | Serious\(^a\) | No serious inconsistency | No serious indirectness | Serious\(^b\) | None | 229 of 255 (89.8%) | 172 of 249 (69.1%) | RR 1.3 (1.19 to 1.42) | 207 more per 1000 (from 131 more to 290 more) | ⊕⊕ OO LOW |
| Leukopenia | Randomized trials | Serious\(^a\) | No serious inconsistency | No serious indirectness | Serious\(^b\) | None | 84 of 237 (35.4%) | 126 of 229 (55%) | RR 0.65 (0.54 to 0.78) | 193 fewer per 1000 (from 121 fewer to 253 fewer) | ⊕⊕ OO LOW |
| Hemoglobin reduction | Randomized trials | Serious\(^a\) | No serious inconsistency | No serious indirectness | Serious\(^b\) | None | 29 of 89 (32.6%) | 44 of 81 (54.3%) | RR 0.6 (0.43 to 0.84) | 217 fewer per 1000 (from 87 fewer to 310 fewer) | ⊕⊕ OO LOW |
| Oropharyngeal mucosal injury (OMI) | Randomized trials | Serious\(^a\) | No serious inconsistency | No serious indirectness | Serious\(^b\) | None | 98 of 165 (59.4%) | 135 of 159 (84.9%) | OR 0.25 (0.15 to 0.44) | 265 fewer per 1000 (from 137 fewer to 391 fewer) | ⊕⊕ OO LOW |
| Nausea and vomiting | Randomized trials | Serious\(^a\) | No serious inconsistency | No serious indirectness | Serious\(^b\) | None | 46 of 157 (29.3%) | 74 of 149 (49.7%) | RR 0.6 (0.45 to 0.8) | 199 fewer per 1000 (from 99 fewer to 273 fewer) | ⊕⊕ OO LOW |

The basis for the assumed risk (e.g., the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

\(^a\)Only one study accurately used the random method, and none of the studies specifically described the allocation concealment and blind method. As it is an objective indicator, it is downgraded one level.

\(^b\)Downgrading a notch was conducted because the number of included studies is small, and the confidence interval is wide.

Abbreviations: CI, confidence interval; KPS, Karnofsky Performance Status Scale; RR, risk ratio.
to stress, intoxication, and other nonspecific damages; norcantharidin can increase active oxygen level, mediate SKOV3 cell apoptosis, as well as G2/M phase periodic arrest. An animal test has confirmed that Aidi injection can inhibit tumor metastasis by reducing the expression of Vimentin and VEGF-A in tumor tissues and increasing the expression of cadherin-1.

For this paper, a meta-analysis was conducted on 9 RCTs of Aidi injection combined with RT for NPC (422 patients). The results showed that compared with RT alone, Aidi injection combined with RT was not different in efficacy for local lesions of NPC (based on the TER). Subgroup analysis on the dose of the TCM injection also showed no difference, indicating that Aidi injection may not reduce the tumor volume. In addition, we evaluated the CRR of patients separately, and it was demonstrated that the experimental group was superior to the control group in the CRR, which indicated that Aidi injection had certain advantages in patients with obvious effects. Considering that the No. of studies is limited, the results are to be further verified by more relevant studies.

KPS score is an indicator reflecting patients’ physical functioning status. In this meta-analysis, the significant difference in KPS score between the 2 groups indicates that Aidi injection did improve the life quality and daily behavior ability of patients.

In terms of adverse reactions, the Aidi injection combined with RT group has more advantages than the RT group. Aidi injection can reduce the toxic and side effects caused by RT. It can improve leukopenia and hemoglobin reduction, and reduce the incidence of OMI, nausea and vomiting. However, it cannot improve the adverse reactions of thrombocytopenia and skin damage.

All the results showed good homogeneity, and the sensitivity analysis showed good stability. The study showed that compared with the RT alone group, the Aidi injection combined with RT group had more advantages in improving the symptoms of patients with NPC and alleviating adverse reactions.

This study has some limitations. First, limited by the quality and quantity of the included trials, more high-quality studies are needed to confirm the above conclusions. Second, the operation of allocation concealment and blinding was not specifically described, and there might be selection bias, measurement bias, or implementation bias. Third, the included studies were all from China, with regional limitations and poor universality.

Conclusion

Current evidence suggests that Aidi injection combined with RT for NPC treatment can improve patients’ KPS score and reduce some toxic and side effects. However, the difference of TER between 2 groups is still yet to be evaluated, and Egger’s test and Begg’s Test did not indicate publication bias.

Author Contributions

Conception and design: Renhong Wan, Anlan Zhao.
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Declaration of Conflicting Interests

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