

A small dose of remifentanyl pretreatment suppresses sufentanil-induced cough during general anesthesia induction: a randomized, double-blind, placebo-controlled trial

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Abstract

Background: Intravenous use of sufentanil can elicit cough. This study aimed to evaluate the inhibitory effect of pre-injection of a small dose of remifentanil on sufentanil-induced cough during the induction of general anesthesia. **Methods:** This prospective, randomized, controlled trial was conducted from January 10, 2019 to March 01, 2019. A total of 100 patients undergoing elective surgery under general anesthesia were enrolled, and at last 84 patients were included and randomly allocated into two equal size groups (n=42): Patients in the Remifentanil group (R group) received an intravenous infusion of remifentanil 0.3 µg/kg (diluted to 2 ml) 1 minute before sufentanil injection; patients in the Control group (C group) received 2 ml of normal saline (NS) at the same time point. Injections of patients in both groups were completed within 5 seconds. Then, sufentanil 0.5 µg/kg was injected within 5 seconds and the number of coughs that occurred within 1 minute after sufentanil injection were recorded. One minute after sufentanil injection, etomidate 0.3 mg/kg and cisatracurium 0.15 mg/kg were given for general anesthesia induction irrespective of the presence or absence of cough. The mean arterial pressure (MAP) and heart rate (HR) at time points just before remifentanil pretreatment administration (T0), 3 minutes after administration (T1), 1 minute after intubation (T2), and 3 minutes after intubation (T3) were recorded. **Results:** The incidence of cough in patients in the R group and C group was 4.8% and 31%, respectively. Compared with group C, the incidence and severity of cough in group R was significantly lower ($P < 0.01$). No significant differences were observed in MAP and HR at the time of general anesthesia induction between the two groups ($P > 0.05$). **Conclusion:** Pretreatment with a small dose of remifentanil effectively and safely reduced the incidence and severity of cough induced by sufentanil during anesthesia induction and can be used as an alternative treatment to inhibit coughing caused by sufentanil.

Background

Sufentanil has been commonly used during general anesthesia induction because of its strong analgesic property (1). However, its intravenous use can elicit cough (1, 2).

This side effect may increase intracranial, intraocular and intraabdominal pressure, which may endanger some special patients such as those with a cerebral aneurysm, open eye injury or abdominal aortic aneurysm.

Various agents have been used for cough suppression prior to induction of general anesthesia including: 1- Intravenous opioid such as fentanyl, 2- intramuscular morphine, 3- Dexmedetomidine, 4- Magnesium sulfate, 5- Terbutaline, 6- lidocaine and 7- Dezocine (1, 3-8).

However, because of their more or less potential additional side effects, long onset time, long duration, inconvenience to get, they were somewhat limited in clinical use.

Remifentanil is an opioid that has both short onset time and short duration and is also readily available.

The use of remifentanyl for cough suppression has been documented in the literature (9-13) in which it has shown effective cough suppression, however, there are few studies in which remifentanyl has been used prior to induction of general anesthesia in order to prevent opioid-induced cough .

Therefore, in this study, we evaluated the effects of remifentanyl on the incidence and severity of sufentanil-induced cough during general anesthesia induction, aiming to assess whether a small dose of remifentanyl could be used as an alternative treatment to inhibit cough caused by sufentanil.

Methods

2.1 Participants

This study passed the ethical review by the Ethics Committee of the First Affiliated Hospital of Wenzhou Medical University (2018-150) and was registered at the Chinese Clinical Trial Registry (ChiCTR1900020587, January 9, 2019). Written informed consents were obtained from all patients.

One hundred patients were screened and at last a total of 84 patients scheduled for elective surgery under general anesthesia, aged 20-70 years old, classified as ASA I or II, were selected (shown as Figure 1).

Exclusion criteria were: smoking; Body mass index (BMI) more than 28; increased intracranial, intraabdominal or inocular pressure before operation; a history of respiratory diseases such as asthma, chronic cough and upper respiratory tract infection in two weeks; a history of other systemic diseases such as gastroesophageal reflux, hypertension, diabetes, heart disease, impaired kidney or liver function; a history of chronic administration of opioids, cough-causing medications such as angiotensin-converting-enzyme inhibitors (ACE-inhibitors) and anti-cough medications such as bronchodilators and steroid therapy.

2.2 Anesthesia and research procedure

The trial was conducted from January 10, 2019 to March 01, 2019 in the operation room of The First Affiliated Hospital of Wenzhou Medical University. None of the patients received any premedication. A 20-gauge cannula was inserted into the dorsum of each patient's hand and connected to a T-connector for drug administration. Standard ASA monitors were attached, including non-invasive arterial pressure, electrocardiography and pulse oxygen saturation (SPO₂). These 84 patients were randomly and equally divided into two groups: R group for remifentanyl 0.3 ug / kg (diluted to 2ml) intravenous infusion; C group for 2 ml of NS. All patients were given oxygen via a face mask (6 L/min) before induction. Injections of both two groups (remifentanyl or saline) were completed within 5 seconds. One minute later, a sufentanil bolus of 0.5ug / kg was injected into every patient within 5 seconds.

The times of cough occurred within 1 minute after sufentanil injection were recorded and the severity was graded depending on the cough times (mild, 1-2; moderate, 3-4; and severe, ≥ 5).

One minute after the injection of sufentanil, etomidate 0.3 mg / kg and cisatracurium 0.15 mg / kg were given for general anesthesia induction irrespective of presence or absence of cough. MAP and HR at each time point of immediately before remifentanil or normal saline administration (T0), 3 minutes after administration (T1), 1 minute after intubation (T2) and 3 minutes after intubation (T3) were recorded.

Side effects of remifentanil such as muscle rigidity or other unintended effects throughout the experiment were also recorded.

2.3 Statistical analysis

Sample size estimates were done using PASS 11 software (PASS, Kaysville, UT, USA). The incidence of cough elicited by 0.5µg/kg of sufentanil in our pilot study was 30% (6/20) and reduced to 5% (1/20) by the pretreatment with remifentanil. To achieve 80% statistical power with $\alpha=0.05$, each group would need no less than 32 patients. To account for drop-outs, we recruited 50 patients in each group.

Patients were randomly and equally divided into two groups by using a computer generated random-number sequence. Suying FU generated the random allocation sequence, Wendong Lin enrolled participants and assigned participants to interventions and Jiehao Sun recorded and assessed the outcomes. Both remifentanil (0.3 ug / kg, diluted to 2ml) and NS were 2 ml which injected by Wendong Lin. Participants and Jiehao Sun were blinded after assignment to interventions.

Measurement data of non-normal distribution (BMI, gestational weeks etc.) were presented as a median (Q1, Q3) and analyzed with the Kruskal-Wallis H test. Categorical data were presented as absolute and relative effect sizes and assessed by the chi-square test or Fisher's exact test as appropriate. Continuous variables at different time points in the groups were compared by using repeated measures design analysis of variance. A value of $P<0.05$ was considered a statistically significant difference.

Data were analyzed by the SPSS software 22.0 (IBM Corp, Armonk, NY). The normality of measurement data distribution was tested by the Shapiro-Wilk test. Normally distributed measurement data such as age and BMI were presented as the mean \pm standard deviation and analyzed using Student's t test. Non-normally distributed data were presented as a median (Q1, Q3) and analyzed using Mann-Whitney U test. Numeration data such as the incidence of cough were presented as absolute or relative effect sizes and analyzed by the χ^2 test. Grade data—the severity of coughs—were analyzed using Mann-Whitney U test. The changes in HR and BP before and after injection between groups were compared using [repeated measures analysis of variance](#).

All statistical analyses were two-tailed and statistical significance was accepted at the 5% probability level.

Results

3.1 Demographic characteristics

The trial was conducted from January 10, 2019 to March 01, 2019. One hundred eligible patients were screened while 84 of them ultimately participated in our study and were included in the final analyses (four of them declined participation; seven of them had unacceptable hypertension before the study started; five patients' anesthetic plans were changed before the study started.) (Figure 1).

ASA physical status and Demographic characteristics including gender, age and BMI of two groups were similar ($P > 0.05$, Table 1).

Table 1. Demographic data.

| Groups | Gender [M/F] | Age [yr] | ASA class (I/II) | BMI [kg/m ²] |
|----------------|--------------|-----------|------------------|--------------------------|
| Group C (n=42) | 16/26 | 43.6±11.4 | 16/26 | 22.5±1.9 |
| Group R (n=42) | 18/24 | 45.6±11.0 | 11/31 | 22.9±2.9 |
| <i>P</i> value | 0.657 | 0.414 | 0.243 | 0.449 |

Values are expressed as mean±standard deviation or number of cases.

No statistical differences were found between groups in gender, age, ASA class or BMI.

R= remifentanyl, C=control; M=male, F=female; ASA=American Society of Anesthesiologists physical status; BMI=body mass index.

3.2 Incidence and severity of cough

The incidence in group C was 31% and in group R was 4.8%. Both the incidence and severity of cough in Group R were significantly lower than those in Group C ($p < 0.05$, Table 2).

Table 2 Incidence and severity of sufentanil induced cough.

| Groups | Incidence of cough (n(%)) | Severity of cough (n(%)) | | | |
|----------------|---------------------------|--------------------------|------|----------|--------|
| | | None | Mild | Moderate | Severe |
| Group C (n=42) | 31 | 69 | 7.1 | 4.8 | 19 |
| Group R (n=42) | 4.8 | 95.2 | 2.4 | 0 | 2.4 |
| <i>P</i> value | 0.002* | | | 0.002* | |

Values are expressed as frequency.

Both the incidence and severity of cough in Group R were significantly lower than those in Group C ($p < 0.05$).

R= remifentanyl; C=control. Severity of cough was graded as mild (1-2), moderate (3-5), and severe (>5) based on the number of cough observed in 60s after sufentanil injection. *Indicates $p<0.01$ Compared with Group C.

3.3 Hemodynamic data changes

There was no statistical difference in the data of HR and NBP between two groups at four corresponding time points ($p > 0.05$, Table 3 and Table 4).

Table 3 Changes of MAP.

| Groups | MAP (mm Hg) | | | |
|---------|-------------|-----------|-----------|-----------|
| | T0 | T1 | T2 | T3 |
| Group C | 94.9±13.8 | 76.2±12.9 | 93.9±20.4 | 82.0±17.0 |
| Group R | 99.0±12.7 | 78.7±13.3 | 95.0±16.5 | 84.7±15.5 |
| P value | P =0.322 | | | |

Table 4 Changes of HR.

| Groups | HR bpm | | | |
|---------|-----------|-----------|-----------|-----------|
| | T0 | T1 | T2 | T3 |
| Group C | 80.0±18.2 | 68.6±16.9 | 77.0±19.0 | 67.7±15.2 |
| Group R | 78.9±11.3 | 67.9±11.0 | 77.8±13.1 | 70.5±10.9 |
| P value | P =0.886 | | | |

Values are expressed as mean±standard deviation.

There were no significant differences in ether MAP or HR between the two groups.

R= remifentanyl, C=control; T0, time before administration of remifentanyl or normal saline; T1: 3 minutes after administration; T2: 1 minute after intubation; T3: 3 minutes after intubation; MAP: mean arterial pressure; HR: heart rate.

3.4 Side effects or unintended effects

There was none patient having apnea, muscle rigidity or other unintended effects in either group.

Discussion

This study demonstrated that pretreatment with remifentanyl at a small dose of 0.3 µg/kg reduced the incidence and severity of sufentanil-induced cough without influencing the hemodynamics during anesthetic induction. The incidence of cough was 31% in group C and decreased to 4.8% in Group R.

Coughing following the administration of opioid drugs during general anesthesia induction is often reported. In this study, the incidence of cough induced by sufentanil was 31%. In an study by Agarwal et al(2) sufentanil 0.3µg/kg injected over 5 seconds elicited cough in 15.8% of patients while in another study by Li et al(14) the incidence of cough was 37% after the injection of sufentanil 0.5µg/kg within 3 seconds. With a high dose of sufentanil (1µg/kg), the incidence of sufentanil-induced cough could be up to 45.8%(1). The various incidence among different studies might be due to the different doses of sufentanil used and the differences in concentrations, administration rate, race and age(1, 15).

Various mechanisms have been proposed to explain opioid-induced cough. A plumonary chemoreflex mediated by either vagal C-fiber receptors close to pulmonary vessels or irritant receptors may play a role in opioid-induced cough (16). Opioid-induced histamine release(17) and muscle rigidity leading to sudden closure of the vocal cords or supraglottic obstruction by soft tissue(18) may be another possible casual factor. In addition, some prior studies found that opioid receptor dualism might also be an important mechanism (3, 8, 19) .

Various pretreatments with drugs such as lidocaine, Terbutaline, Dezocine, Dexmedetomidine and Magnesium sulfate have been reported to reduce the incidence of opioid-induced cough(1, 5, 6, 8, 20), but all of these drugs might add variable extra side effects and potential risks. In a study of He et al. (5), injection of dexmedetomidine 0.5 µg/kg or 1.0 µg/kg over 10 min inhibited the cough induced by the following fentanyl (4 µg/kg) intravenous push. However, this dose of dexmedetomidine has the potential to cause bradycardia and hypotension, and the too long injection time is also a problem. In another study (1), 30 or 50 mg/kg of MgSO₄ inhibited the cough induced by the following 1.0 µg/kg of sufentanil, but several patients dropped out the study due to an obvious burning sensation during the injection of MgSO₄ and the injection of MgSO₄ could also increase the plasma magnesium level. Inhalation of terbutaline (5 mg in 2 ml normal saline; via a jet nebulizer) fifteen minutes before bolus fentanyl (5µg/kg, iv) has also been reported to be able to inhibit cough (6), but the inaccessibility of terbutaline, long operating time, and complicated operation are the limitations of this method. Injecting lidocaine 0.5 mg/kg has also been proved effective to suppress fentanyl-induced cough (20) , but its cardiac inhibition may be a potential risk. Dezocine 0.1 mg/kg 2 min prior to intravenous sufentanil (0.5 mug/kg) can also

effectively suppress fentanyl-induced cough(8), but in short surgeries, the excessive sedation time of this dose of dezocine may be a problem.

Some other studies used a pre-emptive small dose of the opioids to inhibit opioid-induced cough which could avoid those additional side effects or potential risks of other kinds of drugs. Hung et al. (4) reported that a pre-emptive small dose of fentanyl (25µg) significantly reduced cough induced by the following 125µg fentanyl and Phua et al.(3) found that intramuscular morphine pretreatment 1 hour before induction could also decrease the incidence of fentanyl-induced cough. However, either fentanyl or morphine has its limits because of long onset or long duration time.

In this study, we found that remifentanyl, an opioid readily available, with both short onset and duration time, could decrease the incidence and severity of sufentanil-induced cough during anesthetic induction.

It has not been very clear that how small doses of opioids inhibit the cough caused by opioids themselves. In the study of Hung et al. (4), a pre-emptive small dose of fentanyl (25µg) significantly reduced cough induced by the following 125µg fentanyl and this phenomenon was thought to be associated with the smaller plasma concentration fluctuation of fentanyl.

However, in this study, we found that a pre-emptive small dose of 0.3 µg/kg remifentanyl could also reduce cough induced by the following 0.5 µg/kg sufentanil though what we used as a pretreatment was another opioid, remifentanyl, not sufentanil itself. Thence, the theory of sufentanil concentration fluctuation in plasma mentioned above seems unlikely to explain the result.

We guess that opioid receptor dualism may be a possible mechanism to partly explain this phenomenon. One of the common and useful side-effects of opioid analgesics is suppression of the cough reflex which is the basis of their use in oral cough suppressants(3). Sufentanil, fentanyl and remifentanyl infusion before recovery from general anesthesia were all also reported to be able to suppress coughing on extubation (9, 21, 22). Opioids may inhibit the cough reflex by a direct effect on the cough center in the medulla, at doses lower than those required for analgesia(3). Therefore, we suppose that the anti-tussive effect of pre-emptive remifentanyl in the present study might be related to this kind of centrally-acting effect. The small priming dose of remifentanyl might have firstly exerted its central anti-tussive effect and then inhibited the cough-inducing effect of the following large dose of sufentanil. This hypothesis was partly supported by the study of Phua et al(3) in which the incidence of fentanyl-induced cough was reduced by intramuscular morphine pretreatment 1 hour before. However, this speculation still lacks definitive evidence; more studies are still needed to verify this hypothesis and to reveal the exact mechanism.

In addition, since remifentanyl has respiratory depression effect, possible apnea related absence of cough after remifentanyl administration must also be considered. It was also possible that the dose of remifentanyl caused a transient apnea that caused us to see absence of coughing. For example, 50~60 seconds for the remifentanyl to reach effect site, apnea for another probably 40~50 seconds and then

resume breathing, which can partially or even almost cover the observation time after the administration of sufentanil.

Remifentanil may induce muscle rigidity and blood pressure and heart rate decline (15). In a study performed by Shen et al (15), three patients in the remifentanil group had muscle rigidity and one had significant bradycardia requiring treatment with atropine. However, in our study, there was none patient had such adverse reactions, which might be due to the very small dose of remifentanil we used.

There was a limitation in our study. As few studies have shown how many doses of remifentanil can be used to suppress cough caused by opioids, we used a dose of remifentanil that was close to the dose of fentanyl used in the study of Hung et al. (4) in which a pre-emptive small dose of fentanyl (25µg) was used to reduce cough induced by the following 125µg fentanyl. Therefore, we only used a single dose of remifentanil, so we couldn't know whether it at different doses such as 0.1 µg/kg–0.2 µg/kg–0.4 µg/kg would be effective in suppressing the cough reflex induced by sufentanil. Further studies need to be done to explore the relationship between dose and the cough suppressing effect of remifentanil.

Conclusion

In conclusion, pretreatment with a small dose of remifentanil can effectively and safely suppress the incidence and severity of cough induced by sufentanil injection during general anesthesia induction and can be used as an alternative treatment to inhibit coughing caused by sufentanil.

Abbreviations

ASA: American Society of Anesthesiologists; NS: normal saline; IV: intravenous; MAP: mean arterial pressure; HR: heart rate; BMI: body mass index; ACE: angiotensin-converting-enzyme; SPSS: Statistical Product for Social Sciences; SPO₂: pulse oxygen saturation.

Declarations

Ethics approval and consent to participate

This study passed the ethical review by the Ethics Committee of the First Affiliated Hospital of Wenzhou Medical University (2018-150) and was registered at the Chinese Clinical Trial Registry (ChiCTR1900020587, January 9, 2019). Written informed consent was obtained from all patients.

Consent for publication

Not applicable.

Availability of data and materials

The dataset supporting the conclusions of this article is included within the article and its additional files.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

WL performed the trial and wrote the manuscript. JS assisted with trial conduct and data analysis. SF designed the study and revised the manuscript. All authors read and approved the final manuscript.

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Additional Files

File name: Additional file 1

Title of data: CONSORT 2010 checklist of information to include when reporting a randomised trial

Description of data: this is a completed CONSORT checklist of this manuscript.

File name: Additional file 2

Title of data: original data

Description of data: this is the dataset supporting the conclusions of this article, including demographic characteristics, severity of cough, hemodynamic changes and side effects or unintended effects.

Figures

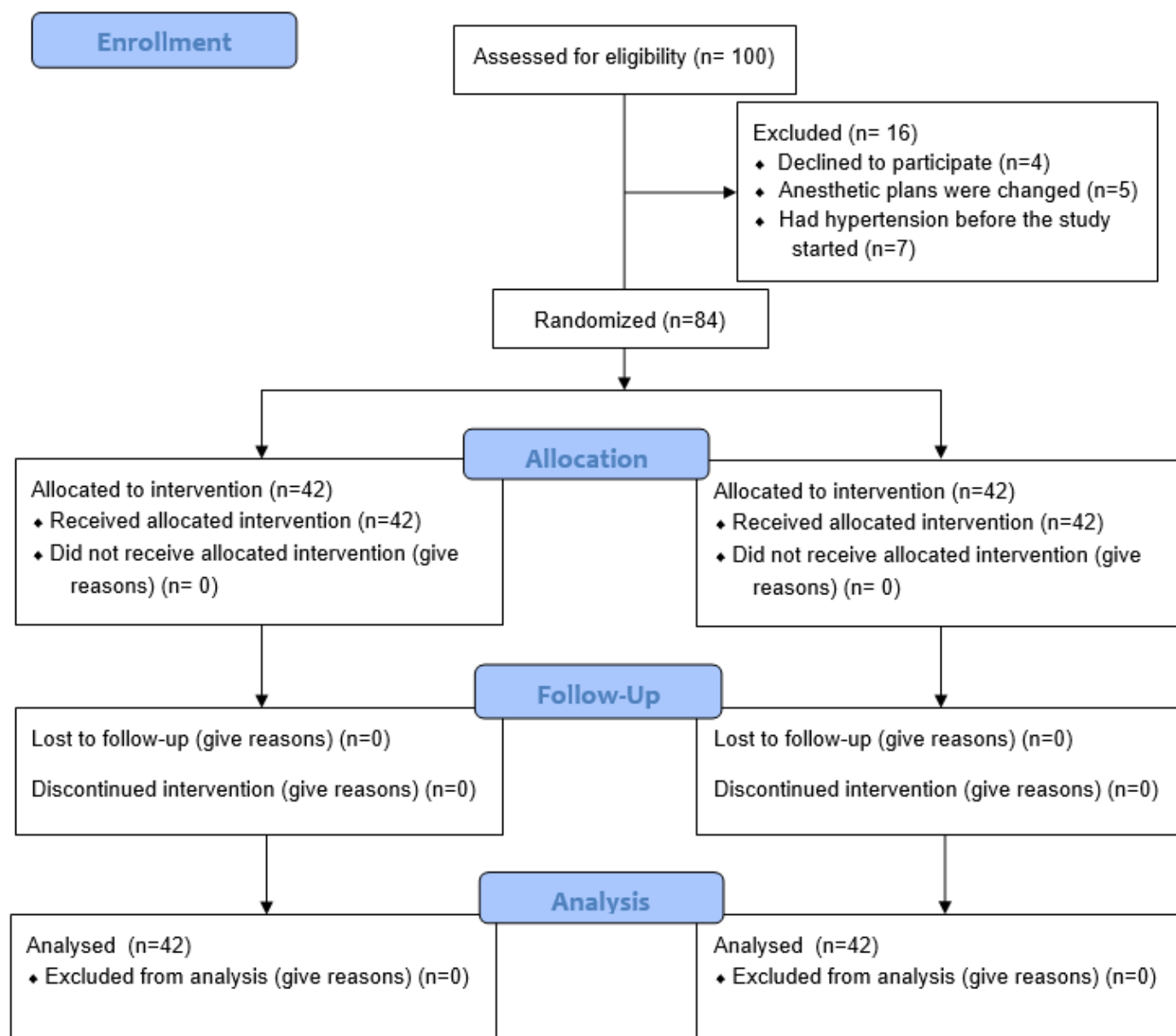


Figure 1

Flow of participants through the study

Supplementary Files

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