臨床疫学研究室

室長 三田英治

臨床疫学研究室は主に消化器疾患の特徴を分子疫学面から検証し、最適な治療方法や安全性を検討しています。代表的な研究内容を示します。

C型肝炎に関しては、ベグインターフェロン・リパビリん併用療法で治療効果を規定したIL-28BのSNPが引き続きインターフェロンフリー治療でも重要な意味を持つかを検討しています。また摂機能低下や腎機能低下症例に対する抗HCV療法の安全性を調査しています。HIV感染合併例でのインターフェロンフリー治療の成果もまとめており、抗レトロウイルス治療との薬物相互作用も検討しています。

次にB型肝炎では、核酸アナログの長期投与成績から導かれる耐性化の問題点を検討しています。そして、ラミブチン・アデホビル併用療法効果不良例に対し、アデホビルをテノホビルに切り替えることの有効性を明らかにしました。近年散発的に発生しているB型急性肝炎ではgenotype Aが大半を占めていますが、その特徴を解析し、慢性化への関与についても検討しています。

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平成26年度 研究結果報告書 灘秀樹

研究課題名
平成22-24年度国立病院機構共同臨床研究によるEBM推進のための大規模臨床研究事業：2型糖尿病を併せ持つ高血圧患者におけるメトホルミンの心肥大・心機能に対する効果の検討

目的
2型糖尿病を併せ持つ高血圧患者を対象とし、メトホルミンを投与した際の心肥大・心機能に対する効果を、心臓超音波検査による左室重量・拡張能、血中不全バイオマーカーを指標として検討する

研究デザイン：医師主導型多施設共同非盲検ランダム化群間並行比較試験

方法：2型糖尿病を併せ持つ高血圧患者にメトグルコを投与する群（220名）と非投与群（220名）。前・6か月・12か月後の心臓超音波検査と血中不全バイオマーカーを測定。

結果
症例登録中。10例の登録を行い10例終了。
Assertive case management versus enhanced usual care for people with mental health problems who had attempted suicide and were admitted to hospital emergency departments in Japan (ACTION-J): a multicentre, randomised controlled trial

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Summary

Background Non-fatal suicide attempt is the most important risk factor for later suicide. Emergency department visits for attempted suicide are increasingly recognised as opportunities for intervention. However, no strong evidence exists that any intervention is effective at preventing repeated suicide attempts. We aimed to investigate whether assertive case management can reduce repetition of suicide attempts in people with mental health problems who had attempted suicide and were admitted to emergency departments.

Methods In this multicentre, randomised controlled trial in 17 hospital emergency departments in Japan, we randomly assigned people aged 20 years and older with mental health problems who had attempted suicide to receive either assertive case management (based on psychiatric diagnoses, social risks, and needs of the patients) or enhanced usual care (control), using an internet-based randomisation system. Interventions were provided until the end of the follow-up period (i.e., at least 18 months and up to 5 years). Outcome assessors were masked to group allocation, but patients and case managers who provided the interventions were not. The primary outcome was the incidence of first recurrent suicidal behaviour (attempted suicide or completed suicide); secondary outcomes included completed suicide and all-cause mortality. This study is registered at ClinicalTrials.gov (NCT00736918) and UMIN-CTR (C000000444).

Findings Between July 1, 2006, and Dec 31, 2009, 914 eligible participants were randomly assigned, 460 to the assertive case management group and 456 to the enhanced usual care group. We noted no significant difference in incidence of first recurrent suicidal behaviour between the assertive case management group and the enhanced usual care group over the full study period (log-rank p=0.258). Because the proportional hazards assumption did not hold, we did ad-hoc analyses for cumulative incidence of the primary outcome at months 1, 3, 6, 12, and 18 after randomisation, adjusting for multiplicity with the Bonferroni method. Assertive case management significantly reduced the incidence of first recurrent suicidal behaviour up to the 6-month timepoint (6-month risk ratio 0.50, 95% CI 0.32–0.80; p=0.003), but not at the later timepoints. Prespecified subgroup analyses showed that the intervention had a greater effect in women (up to 18 months), and in participants younger than 40 years and those with a history of previous suicide attempts (up to 6 months). We did not identify any differences between the intervention and control groups for completed suicide (27 [6%] of 460 vs 30 [7%] of 454, log-rank p=0.660) or all-cause mortality (46 [10%] of 460 vs 42 [9%] of 454, log-rank p=0.698).

Interpretation Our results suggest that assertive case management is feasible in real-world clinical settings. Although it was not effective at reducing the incidence of repetition of suicide attempts in the long term, the results of our ad-hoc analyses suggested that it was effective for up to 6 months. This finding should be investigated in future research.


Introduction Non-fatal suicide attempt is the most potent predictor of later suicide. Hospital admissions because of attempted suicide and self-inflicted injury have been increasing worldwide. The average number of admissions to emergency departments for attempted suicide and self-inflicted injury per year in the USA more than doubled from about 244000 in 1993–96 to 538000 in 2005–08. In the UK, roughly 220000 patients are admitted to hospital for self-harming annually. Emergency department admission for attempted suicide is therefore increasingly recognised as an opportunity for medical personnel to intervene to prevent future suicide attempts. Several randomised controlled trials have been done to assess the effectiveness of contact interventions (letters or
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See Online for appendix

postcards, telephone calls, home visits, etc) to prevent repetition of suicide attempts.\(^4\) However, no strong evidence has been produced for the effectiveness of this type of intervention.\(^5\) In their systematic review,\(^6\) O'Connor and colleagues showed that psychotherapy reduced suicide attempts in some high-risk adults in populations and settings relevant to primary care. In a randomised controlled trial,\(^7\) cognitive therapy was effective at preventing suicide attempts in adults who had recently attempted suicide. However, the evidence overall is unclear, and the extent to which such findings are applicable to suicidal patients who are admitted to emergency departments is unknown.

Although most suicidal patients who are admitted to emergency departments are suffering from mental health problems, these patients often do not receive adequate mental health-care management in their communities after discharge.\(^8,9\) In a randomised controlled trial, Morthorst and colleagues\(^10\) examined the effects of assertive and intensive case management on repetition of suicide attempts, but the intervention did not lead to a significant reduction in this outcome; however, the study had a small sample size, patients were from a single centre, and individuals with psychosis were excluded from the study.

In this study, we aimed to investigate whether assertive and continuous case management could reduce the incidence of repetition of suicide attempts in adults with mental health problems who had attempted suicide, compared with enhanced usual care.

Methods

Study design and participants

ACTION-J was a multicentre, randomised controlled trial done at 17 Japanese hospitals (appendix) with both an emergency department and a psychiatric department. Potential study participants were adults (aged 20 years and older) who had attempted suicide and were admitted to the emergency department to receive critical care. To be eligible, patients had to have a primary diagnosis of an axis I psychiatric disorder, because the case management intervention was developed for patients with these disorders. Psychiatric diagnosis was obtained by structured interview with the Mini-International Neuropsychiatric Interview,\(^11\) and defined as axis I in accordance with the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR).\(^12\) We excluded patients who had a primary diagnosis that did not meet the definition of a DSM-IV-TR axis I disorder.

Action in anticipation of death was confirmed at least twice in each patient by use of the Suicide Intent Scale.\(^13\) Patients had to be able to understand the description of the study, provide informed consent, attend a face-to-face interview and a session for psychoeducation during their stay at the emergency department before enrolment in the study, and visit the participating hospital regularly to attend face-to-face interviews for assessments and case management after discharge from the emergency department.

The study protocol was approved by the Central Research Ethics Committee of the study sponsor (Japan Foundation for Neuroscience and Mental Health, Tokyo, Japan) and by the local ethics committees of all participating hospitals. All participants provided written informed consent.

Randomisation and masking

Participants were randomly assigned (1:1) by an internet-based system operated by a central, independent data centre to either the intervention group (assertive case management) or the control group (enhanced usual care). Assignment was by the minimisation method, with four factors: participating hospital, sex, age (younger than 40 years vs 40 years and older), and history of previous suicide attempts before the current episode. We regarded these as factors that could affect the study outcomes.

Outcome assessors were masked to group assignment, but patients and case managers who provided the interventions were not. The outcome assessors, who were trained for the assessments before the trial, collected the information about attempted suicide from participants or their family members by direct interview. The assessors did not know the participants' assigned groups, the status of implementation of the intervention, or information about events obtained by other on-site staff. An event review committee independently assessed all events related to the study outcomes.

Procedures

After patients were physically stabilised and alert consciousness was confirmed, potential study participants received thorough psychosocial assessment, including assessment of the social, psychological, and motivational factors specific to the self-harm event and an assessment of mental health, social risks, and needs, as recommended by UK national clinical practice guidelines.\(^14\) Trained psychiatrists in the study group checked the patients against the inclusion and exclusion criteria, and provided a complete description of the study. Next, psychiatrists or other trained medical personnel from the study group gave the patients semi-structured psychoeducation, as suggested by WHO.\(^15\) After the psychoeducation session, patients were provided with the complete study description again before being asked to provide informed consent. Assigned interventions were provided until the end of the follow-up period (ie, at least 18 months and up to 5 years).

Participants who were randomly assigned to the control group received enhanced usual care at the participating emergency departments.\(^16\) In addition to the psychoeducation session in the emergency department before randomisation, these participants were given an information pamphlet listing available social resources (health care-based and local government services) every time they visited for periodic assessments (6 months and
18 months after randomisation, then annually until the end of the study. Participants who were randomly assigned to the intervention group were offered assertive and continuous care management (panel 1), delivered by dedicated case managers who were trained experts in mental health (psychiatrists, nurses, social workers, or clinical psychologists). Encouragement to participate in psychiatric treatment was a core feature and appointments with psychiatrists and primary care physicians were organised. To facilitate the case management, the psychoeducation was also provided to participants' family members during the participants' initial stay in the hospital.

The case management was provided in accordance with a manual developed by the intervention programme committee of the study group. Briefly, the case managers periodically contacted participants assigned to the intervention group for 18 months after randomisation (at weeks 1 and at weeks 1, 2, 3, 6, 12, and 18) during their stay at the emergency department and after discharge. When applicable, the case managers contacted the participants every 6 months until the end of the trial (June 30, 2011). In principle, case management was accomplished through direct dialogue (face-to-face interviews by the case managers at the hospital), or by telephone conversation as the next best option. When case managers could not reach participants, they approached family members who had given their consent in advance to be contacted; the frequency with which this approach was used was not monitored. To maintain the quality of the standardised intervention, the intervention programme committee (which consisted of the case managers and a group of the study investigators) held case conference meetings every 2 months (fidelity scores were not calculated). The committee also visited the participating hospitals when necessary. The protocol specified two interim analyses to assess the primary outcome, the first at roughly two-thirds into enrolment, and the second at the end of enrolment. An independent data monitoring committee reviewed safety and efficacy issues from the interim analyses and from periodic monitoring reports.

**Panel 1: Features of the assertive care management intervention**

- Periodic contact (either face-to-face or by telephone) with participants during their stay in the emergency department and after discharge
- Collection of information about each participant's treatment status and social problems that could disturb their treatment adherence
- Encouragement of participants to adhere to psychiatric treatment
- Coordination of appointments with psychiatrists and primary care physicians
- Encouragement of participants who discontinued psychiatric treatment to return to treatment
- Referrals to social services and private support organisations, and coordination for use of these resources to accommodate the individual needs of patients
- Provision of the psychoeducation content and information about social resources through a dedicated website

**Figure 2: Trial profile**

DSM-IV-TR=Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision. **Some participants were excluded for more than one reason.**
produced every 3 months throughout the study period (under masking).

Outcomes

The primary outcome measure was the incidence of first recurrent suicidal behaviour (attempted suicide or completed suicide). We also measured incidence of completed suicide and all-cause mortality as secondary outcomes to support the primary outcome measure. Because our data for the primary outcome presented time-dependent effects (the proportional hazard assumption did not hold), we also measured the cumulative incidence of the first episode of recurrent suicidal behaviour at 1, 3, 6, 12, and 18 months after randomisation as ad-hoc analyses. Information about participant deaths was obtained by the outcome assessors or from the Government death registry.

Other protocol-specified secondary outcomes were number and incidence of recurrent suicidal behaviours, including repeated suicidal attempts per person-year; number of self-harm behaviours; types and numbers of people or organisations to consult; other medical services (clinical visit or hospital admission); physical function; Beck Hopelessness Scale score; and Health Survey for quality-of-life score (short form-36). We plan to publish results for all these outcomes in a separate report.

Statistical analysis

We estimated that the annual incidence of first recurrent suicidal behaviour would be 15% in the control and 10-5% in the intervention group. Based on these estimates, we calculated that the minimum number of participants needed per group to confirm the superiority of the assertive case management intervention (with an α of 0.05 and a statistical power of 90%) was 421. In anticipation of withdrawals and missing data, we aimed to recruit 910 participants to the study.

Analyses were done in accordance with the intention-to-treat principle. To check the assumption of proportional hazards for the primary outcome, we generated an overall cumulative incidence curve using the Kaplan-Meier method and log-log plot. Because our data presented time-dependent effects (the proportional hazards assumption did not hold), the hazard ratio in the survival analysis was not appropriate as a measure of effects. Therefore, we calculated risk ratios (RRs) with 95% CIs for cumulative incidence at five timepoints as ad-hoc analyses; for comparison with the results obtained from previous reports, we selected months 1, 3, 6, 12, and 18 after randomisation. We set α at 0.008 for adjustment of multiplicity by the Bonferroni method.

We did regression analyses for the calculated RRs. We also made adjustments by using regression models with the randomisation factors: sex (male vs female), age (younger than 40 years vs 40 years and older), and history of previous suicide attempts before the current episode (yes vs no). In sensitivity analyses, we did multiple imputations for missing data (at the ad-hoc timepoints) and used regression models to adjust for the randomisation factors.

We did prespecified subgroup analyses of the primary outcome (using the ad-hoc analyses for the five specified timepoints) by sex (male vs female), age (younger than 40 years vs 40 years and older), and history of previous suicide attempts before the current episode (yes vs no).

<table>
<thead>
<tr>
<th>Asserive case management group (n=410)</th>
<th>Enhanced usual care group (n=434)</th>
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</thead>
<tbody>
<tr>
<td>Women</td>
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<tr>
<td>Mean age (years)</td>
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<td>Mood disorder</td>
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<td>Adjustment disorder</td>
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<tr>
<td>Other</td>
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<tr>
<td>Visited a psychiatrist within 1 month before the suicide attempt</td>
<td>260 (57%)</td>
</tr>
<tr>
<td>Visited a physician other than a psychiatrist within 1 month before the suicide attempt</td>
<td>151 (33%)</td>
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<tr>
<td>Education</td>
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<tr>
<td>Less than high school</td>
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<tr>
<td>High school</td>
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<tr>
<td>Beyond high school</td>
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<td>Employment status</td>
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<tr>
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<td>Divorced</td>
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<td>Widowed</td>
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<tr>
<td>Lives with partner or family</td>
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<td>Previous suicide attempts</td>
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<td>None</td>
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<td>One or two times</td>
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<tr>
<td>Three or more times</td>
<td></td>
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<tr>
<td>Method of the present suicide attempt</td>
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</tbody>
</table>

Data are n (%) or mean (SD). *One individual with missing data excluded from percentage calculation. **Three individuals with missing data excluded from percentage calculation. Totals are greater than 100% because some individuals used more than one method.

Table 1: Baseline characteristics.
Because of the exploratory nature of the subgroup analyses, we did not make any adjustment for multiplicity. We also did a post-hoc regression analysis in each subgroup analysis to investigate the effect of the remaining randomisation factors (sex, age, and previous suicide attempts) on the primary outcome (by timepoints).

This study is registered at ClinicalTrials.gov (NCT00736918) and UMIN-CTR (C000009444).

Role of the funding source
Neither the funder nor the sponsor of the study had any role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results
Of 6123 emergency admissions after suspected suicide attempt at participating hospitals between July 1, 2006, to Dec 31, 2009, 914 participants were enrolled in the study, of which 460 were randomly assigned to the intervention group (assertive case management) and 554 to the control group (enhanced usual care; figure 1). Baseline characteristics were well balanced between the groups (table 1). As planned in the protocol, two interim analyses were done during the study period (October, 2007, and June, 2008). The results of these analyses were reviewed by the independent data monitoring committee, but conclusive findings were not obtained (data not shown) and the trial was continued until the end of the study period.

The assertive case management group had fairly good adherence to the intervention at the end of the trial (figure 1): 320 (70%) of 460 participants were contacted at least seven times by a case manager. 11 (1%) participants in the assertive case management group did not receive the intervention.

With respect to the primary outcome of incidence of first recurrent suicidal behaviour, there was no difference between the two groups at the end of the study; the survival curve for the assertive case management group was not significantly different from that for the control group (log-rank p=0.258, Wilcoxon p=0.103; figure 2). However, in the ad-hoc analyses at selected timepoints (done because the proportional hazards assumption was not met), the cumulative incidence of first recurrent suicidal behaviour was significantly lower in the intervention group than in the control group at 1, 3, and 6 months after randomisation, but not at 12 or 18 months (table 2).

With respect to the secondary outcomes assessed in support of the primary outcome, we did not identify any differences between the intervention and control groups for completed suicide (27 [6%] of 460 vs 30 [7%] of 554, log-rank p=0.660) or all-cause mortality (46 [10%] of 460 vs 42 [9%] of 554, log-rank p=0.698).

In the subgroup analyses, the intervention group had a significantly lower cumulative incidence of first recurrent suicidal behaviour in women (up to 18 months), and in participants younger than 40 years (up to 6 months), and those with a history of previous suicide attempts (up to 6 months). We noted no significant effect of the intervention in the other subgroups, apart from participants with no history of previous suicide attempts at 6 months only (table 3).

In the sensitivity analysis for the primary analysis, which we did to investigate possible selection bias caused by missing data, we did not find any differences from the results obtained from the primary analysis when adjusted with randomisation factors (sex, age, and previous suicide attempts; table 2), nor from the results obtained from the subgroup analyses (table 3). The sensitivity analysis in the subgroup analysis, which we did to investigate possible selection bias caused by missing data, likewise showed no differences when adjusted for remaining randomisation factors (sex, age, and previous suicide attempts; table 3).

Discussion
Our results show that assertive and continuous case management based on psychiatric diagnoses, social risks, and needs of adults who had attempted suicide was not effective at reducing the risk of repetition of suicide attempt over the full study period (follow-up time from 18 months to 5 years dependent on time of entry to the study), but it did seem to be effective for up to 6 months in our ad-hoc analyses by time from randomisation (panel 2).

Our findings are partly consistent with the results of Morthorst and colleagues' randomised controlled trial in a single Danish hospital.25 They implemented case management through assertive outreach with eight to 20 outreach consultations over 6 months by specialist nurses to
improve adherence with after-treatment as an add-on to standard treatment. The intervention did not show a significant reduction of repetition of suicide attempt at 12 months (OR 0.69, 95%CI 0.34–1.43).

In our trial, adherence to the intervention was 70% (figure 1). After 6 months, the case management was provided every 6 months until the end of the follow-up period (i.e., from 18 months to 5 years after randomisation), whereas before 6 months it was provided more often.

The less frequent intervention after 6 months might have weakened the effectiveness of the intervention, although intervention might be effective only for a short period of time. Our results suggest that continuous case management needs to be taken over by community mental health caregivers within 6–12 months, dependent on the availability of medical and social resources in the community.

Because of the high adherence to our intervention programme and the fact that the trial design was embedded in real-world clinical settings, our study shows that the assertive case management intervention is feasible in clinical practice, with social workers or medical personnel playing the part of case managers. Our findings could also be relevant outside of Japan, in other countries with functioning emergency services and comprehensive mental health care services in place.

The subgroup analyses showed that greater effects were seen in women, participants younger than 40 years, and those with a history of previous suicide attempts. Patients attempting suicide constitute a heterogeneous group, differing in age, livelihood conditions, and risk factors. Further research is needed to examine why a greater effect was seen in these specific subgroups.

We noted no difference in the incidence of completed suicide between groups during the overall study period. In their randomized trial, Fleischmann and colleagues reported significantly fewer deaths by suicide among people who had attempted suicide who were given brief intervention and contact than among those given treatment as usual at the 18-month follow-up. However, their trial was deliberately done in five low-resource countries with little infrastructure and scarce financial and human resources. They noted that treatment was usual for the participating sites in their study "would not cover routine or systematic psychiatric or psychological assessment or help", whereas in Japan psychiatric consultation was available at 76% of the registered tertiary emergency medical centres in 2012, although only some of these centres provided routine psychiatric assessment.

Our study had some limitations. First, the enhancement of usual care might have affected the overall results of our study, since the control group received better care than is usual in clinical practice in Japan. We chose to use enhanced usual care as the comparison group for ethical reasons; however, this approach might have reduced the difference in the primary outcome between the assertive case management group and the control group.

Another limitation of our study is that it did not include suicidal patients younger than 20 years. These patients were excluded because individuals younger than 20 years are regarded as minors in Japan and informed consent has to be obtained from legal guardians. Additionally, we excluded suicidal patients without an axis I DSM-IV-TR disorder as their primary diagnosis because the intervention was designed specifically for patients with an axis I disorder.

Many individuals who had attempted suicide did not participate in the study because their physical conditions were too severe for them to understand the description of the study, and to attend the interview and session for psychoeducation. Additionally, we missed some people who had attempted suicide for eligibility review or contact for the informed consent because of their short hospital stay. Our results might have some selection bias; we could not collect data for people who did not participate in our study because of ethical restrictions. However, the characteristics of our study participants were similar to those described in a national registry study.

Although the outcomes were systematically collected from participants and official records, our results might have some reporting bias. Additionally, we could not compare the self-reported outcome of suicidal behaviour by participants with register data for admissions to emergency wards for critical care or hospital contacts because it was impossible to track all register data or hospital contacts since the catchment areas of some emergency services in urban areas in Japan overlap, and
<table>
<thead>
<tr>
<th>Sex</th>
<th>1 month</th>
<th>3 months</th>
<th>6 months</th>
<th>12 months</th>
<th>18 months</th>
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<tr>
<td><strong>Men (n=400)</strong></td>
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<tr>
<td>Intervention vs control</td>
<td>2/200 (1%) vs 4/184 (1%) vs 10/278 (1%) vs 18/272 (1%) vs 24/278 (1%) vs 25/277 (1%)</td>
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<tr>
<td>Intervention vs control</td>
<td>2/200 (1%) vs 4/184 (1%) vs 10/278 (1%) vs 18/272 (1%) vs 24/278 (1%) vs 25/277 (1%)</td>
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<tr>
<td>Unadjusted risk ratio</td>
<td>0.69 (0.12-1.74) vs 0.48 (0.15-1.74) vs 0.65 (0.13-1.74) vs 0.91 (0.50-1.74) vs 1.01 (0.50-1.74)</td>
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<tr>
<td>Risk ratio (imputed)*</td>
<td>0.79 (0.13-4.66) vs 0.46 (0.14-4.66) vs 0.61 (0.29-1.28) vs 0.88 (0.48-1.61) vs 0.99 (0.59-1.67)</td>
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<tr>
<td>Risk ratio (adjusted)†</td>
<td>0.70 (0.13-4.66) vs 0.48 (0.15-1.74) vs 0.64 (0.30-1.74) vs 0.90 (0.50-1.62) vs 0.99 (0.60-1.66)</td>
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<tr>
<td>Risk ratio (imputed plus adjusted)†</td>
<td>0.76 (0.13-4.48) vs 0.45 (0.14-4.48) vs 0.60 (0.28-1.27) vs 0.87 (0.48-1.57) vs 0.96 (0.57-1.62)</td>
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<tr>
<td>Intervention vs control</td>
<td>3/254 (1%) vs 3/246 (1%) vs 15/273 (1%) vs 27/275 (1%) vs 46/208 (1%) vs 31/213 (1%)</td>
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<tr>
<td>Intervention vs control</td>
<td>3/254 (1%) vs 3/246 (1%) vs 15/273 (1%) vs 27/275 (1%) vs 46/208 (1%) vs 31/213 (1%)</td>
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<tr>
<td>Unadjusted risk ratio</td>
<td>0.07 (0.01-1.56) vs 0.13 (0.04-1.56) vs 0.43 (0.24-1.76) vs 0.62 (0.39-1.76) vs 0.66 (0.44-1.76)</td>
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<tr>
<td>Risk ratio (imputed)*</td>
<td>0.07 (0.01-1.56) vs 0.13 (0.04-1.56) vs 0.43 (0.24-1.76) vs 0.62 (0.39-1.76) vs 0.66 (0.44-1.76)</td>
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<tr>
<td>Risk ratio (adjusted)†</td>
<td>0.07 (0.01-1.56) vs 0.13 (0.04-1.56) vs 0.43 (0.24-1.76) vs 0.62 (0.39-1.76) vs 0.66 (0.44-1.76)</td>
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<td>Risk ratio (imputed plus adjusted)†</td>
<td>0.08 (0.04-0.55) vs 0.12 (0.04-0.55) vs 0.42 (0.24-0.74) vs 0.61 (0.38-0.96) vs 0.63 (0.42-0.95)</td>
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<td><strong>Age</strong></td>
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<tr>
<td>Intervention vs control</td>
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<td>Intervention vs control</td>
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<td>Unadjusted risk ratio</td>
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<td>Risk ratio (imputed)*</td>
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<tr>
<td>Intervention vs control</td>
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<td>Intervention vs control</td>
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<td>Unadjusted risk ratio</td>
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<td>Risk ratio (imputed)*</td>
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<tr>
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<tr>
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<td>Risk ratio (imputed plus adjusted)†</td>
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</table>

Data are number of events/population for the intervention (assumes case management) group or control (enhanced usual care) group, or risk ratio (95% CI). * Risk ratios with data imputed for individuals who missed the assessment. Risk ratios adjusted by use of regression models for the randomisation factors of sex, age, and history of previous suicide attempts before the current episode. Risk ratios with data imputed for individuals who missed the assessment and adjusted by use of regression models for the randomisation factors of sex, age, and history of previous suicide attempts before the current episode.

**Table 3:** First recurrent suicidal behaviour (attempted suicide or completed suicide), by subgroup (ad-hoc analysis by timepoint)
Panel 2: Research context

Systematic review

We searched PubMed for articles published from Jan 1, 1949, to Feb 28, 2014, using the search terms "suicide" OR "self-harm" OR "self-injury" AND "random" OR "interventions". We identified 12 relevant systematic reviews of randomised trials; the most recent systematic review was by O'Connor and colleagues, which showed that psychotherapy reduced suicide attempts in some high-risk adults in populations and settings relevant to primary care. In a recent randomised trial, Morthorst and colleagues examined the effects of assertive and intensive case management on repetition of suicide attempt, but the intervention did not lead to a significant reduction in repetition of suicide attempt.

Interpretation

In our large, multicentre, randomised controlled trial assertive case management was feasible in real-world clinical settings for suicidal patients with psychiatric disorders admitted to the emergency department. Although it was not effective at reducing the incidence of repetition of suicide attempts in the long term, the results of our ad-hoc analyses suggested that it was effective for up to 6 months. Our results also suggest potentially heterogeneous effects of assertive case management; the intervention seemed to be more effective in women, participants younger than 40 years, and those with a history of previous suicide attempts.

some participants might have moved out of the catchment areas. Finally, although outcome data were collected by trained assessors, possible variability of the assessments might have introduced bias into the results.

Contributors

YHit, CK, TA, NI, and NY conceived and designed the study. YHit was the principal investigator. YHit, CK, KO, YO, KI, AS, HM, YHit, Alwak, TK, JA, NH, HH, NH, NI, MK, Alwak, MM, and TA enrolled patients. YHit, CK, KO, YK, YO, KI, AS, HM, YHit, Alwak, TK, JA, NH, HH, NE, NI, MK, Alwak, MM, and TA managed the study at the participating sites. NI and NY analysed the data. CK wrote the first draft of the report. YHit, TA, KO, YK, YO, KI, AS, HM, YHit, Alwak, TK, JA, NH, HH, NE, NI, MK, Alwak, MM, and TA contributed to the writing of the report.

Declaration of interests

We declare no competing interests.

Acknowledgments

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厚生労働科学研究委託事業 難治性疾患実用化研究事業
「特発性大腿骨頭壊死症の治療法確立と革新的予防法開発にむけた全国学際研究」

大腿骨頭壊死症に関する薬物予防治療に関する研究、人工股関節等の外科的治療に関する研究がおこなわれており。当院の関わりとしては、当該疾患の外科的治療の成績の長期追跡調査から外科的治療の有効な選択を明らかにする目的で本事業の中におかれた人工関節治療 registry に症例を登録することで寄与している。現在 210 例の患者登録をしており、当該事業のデータの根幹となっている。

厚生労働科学研究補助金 難治性疾患等政策研究事業
「特発性大腿骨頭壊死症の疫学調査・診断基準・重症度分類の改訂と診療ガイドライン策定を目指した大規模多施設研究」

特発性大腿骨頭壊死症の疫学については過去に報告は多数あったが、バイアスのかかった一面的な解析データが主であったため、正確な統計学的手法を用い、その疫学を明らかにしようとする研究事業であり、本年度から全国疫学調査が開始となっている。当院はその対象施設となっており、今後データの供出によって本事業に貢献していく予定ある。
PCPS システムにおけるキャピテーションによる気泡発生の検討

国立病院機構 大阪医療センター 臨床工学技士
藤井 順也

I．緒言
経皮的肺補助法（PCPS：Percutaneous Cardio Pulmonary Support system）は、クリティカルケア領域で心肺機能の補助として広く用いられている。PCPS では、患者から脱血した静脈血が遠心ポンプに送られ、そこから人工肺で酸素化されたのち患者の動脈へ返血される。その際、遠心ポンプ内では、プロペラが高速で回転することにより生まれる遠心力を利用して血液を送りだしているが、ひとたび脱血不良の状態におかれるとキャピテーションによる気泡発生を誘発することは広く知られている 1,2,3）。しかし、臨床上 PCPS 使用中の脱血不良は避けられない事象である。閉鎖型回路である PCPS において回路内に空気が混入すると、脳などの毛細血管へ直接送られ重篤な空気塞栓症を引き起こす危険性があるが、キャピテーションによる気泡は目視で確認できないほど小さいため 4,5）放置されることが多く、その危険性が重要視されていない。本研究ではキャピテーションによる気泡発生の程度、PCPS の設定条件との関連性を検討したので報告する。

II．方法
1．実験回路
実験回路図を図 1 に示す。実験溶液には、模擬血液としてグリセリン（分子量 92Da, 和光純薬、大阪）を Reverse Osmosis water（RO 水）に溶解し、40vol%グリセリン水溶液になるように調整した。PCPS 回路は、熱交換器付回路（テルモ EBS 回路、テルモ株式会社、東京）を使用し、気泡計測器（ultrasonic Bubble Detector CMD-20, Hatteland Inc, norway）を用いて、遠心ポンプ入口側（脱血側）と人工肺出口側（送血側）にて発生する気泡を測定した。閉塞率の調整には、オクルーダー（HAS II - RE, 泉工医科工業, 埼玉）を使用。送血カニューレは、経皮的挿入カニューレ（カニューレ（CBAS）、Medtronic Inc, 米国）脱血 23Fr, 送血 15Fr, 17Fr, 19Fr を使用した。また、回路内には、十分な除泡を行うためリザーバーを設置した。

図 1 実験回路構成
2. 実験条件
実験の各種条件の組合せを図2に示す。基本条件として、人工肺に流すガス（Flow: 3.0L/min, FiO2: 60%）、回路内温度を36.0℃に設定し、これを基にFlow, FiO2温度を1つずつ変化させた。これに遠心ポンプの回転数と回路閉塞率の各条件を変化させた全ての組合せ375通りについて、送血管の3サイズ（15, 17, 19Fr）の変更を加えた975通り全てにおける気泡発生についてのデータ採取を行った。各々の詳細に付いては以下に述べる。

2-1. ガス条件と温度変化
人工肺に流すガス流量を1, 3, 5, 7, 10L/minの5段階に変化させ、同様にFiO2も21, 40, 60, 80, 100%の5段階に変化させた。また、回路内温度についても10, 20, 30, 36, 37℃の5段階に変化させた。ただし、1つの条件を変更する際は他の条件を基本条件に戻すこととした。

2-2. 回転数と閉塞率の変化
回転数は、1000から3000rpmまで500rpmごとの5段階に変化させ、同様に回路の閉塞率についても20〜100%までの20%ごとの5段階に変化させた。気泡測定条件は、全ての組合せについて10秒間し各々5回ずつ測定した。

III. 結果
各種条件における測定結果を表1に示す。気泡（パブル）発生については、ガス条件や温度変化に比べ回転数と閉塞率を変化させた場合に発生率が高かった。また、脱血側と送血側では、脱血側でより多くのパブル数を認めたため脱血側での回転数と閉塞率を基に気泡発生条件を整理し、ガス条件と温度変化について解析を行った。また、脱血側と送血側でのパブル数との関係性については、人工肺での気泡除去との関係が考えられるため別途解析を行った。詳細を以下に示す。

1. 回転数と閉塞率が気泡発生におよぼす影響
回転数とパブル数の関係を図3に示す。回転数とパブル数の関係を見ると送血管の太さに関する関係なく回転数の増加にともないパブルの数は正比例的に増加し、2500rpm以上では明らかにパブル発生を認める傾向が強かった。また、閉塞率をみると閉塞率を増すごとにパブル数は増加し、その後閉塞率80%で最大を迎え閉塞率100%では収束する結果となった。しかし、パブル発生時のパブル数にはパラつきがあり、他の条件が関与することを示唆する結果となった。

2. 回転数と模擬血液流量の関係
回転数と模擬血液流量の関係性を図4に示す。回転数と流量の関係を見ると閉塞率や送血管の太さに関係なく全ての条件において回転数の増加に伴い流量の増加を認めた。また、これらの関係性について回帰分析を行ったところ高い寄与率を示し強い正の相関を示す結果となった。

3. 係数とパブル数の関係
回転数と流量の関係性において強い正の相関を認めたことから流量を回転数で除して求められたものを係数とし、係数とパブル数の関係性について図5に示した。図5における回転数については図3より明らかにパブル発生を認めた回転数2500rpm以上の関係性についてのみ示している。図5よりパブル数が増大する係数値は0.8〜1.4（mL / rpm・min）の範囲で集中しており、回転数と流量の2つの要素を含む係数がパブル数におよぼす影響に大きく関与することが示された。また、送血側と脱血側での比較においてもパブル数での若干の差は認め
<table>
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<td>0.5</td>
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<tr>
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<td>Y</td>
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<td>Z</td>
<td>0.3</td>
<td>0.4</td>
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表1 各条件における測定結果
<table>
<thead>
<tr>
<th>回転数</th>
<th>開度率</th>
<th>開度率の関係</th>
<th>出血量の関係</th>
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<tbody>
<tr>
<td>15Fr</td>
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<td></td>
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<tr>
<td>17Fr</td>
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<tr>
<td>19Fr</td>
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図3 回転数とパルス数の関係
図4 回転数と模擬血液流量の関係
図5 係数とバブル数の関係
られるもののバブルの発生する係数範囲については同値を示す結果となった。

4. 各種条件で係数範囲に与える影響
図5で求めたバブル数が多く発生する係数範囲について、基本設定、ガス条件（流量、
FiO₂）、温度変化が係数範囲に影響を及ぼさないか統計学的処理（p<0.05，Tukey-Kramer
法）を行ったところ温度変化でのみ若干の有意
差を認めるとの結果となった。

IV. 考察
これまでPCPS使用中のキャビテーションによるマイクロバブルの発生については、色々な
報告がなされ40)、気泡の発生対策40)やその危
険性1011)についても検討されてきた。しかし
その原因について多くの場合、脱血不良や回路
閉塞等、原因は明らかであるが、これまで具体
的に指標とする検討は少なかった。

今回の調査結果では、まず回転数と閉塞率の
関係性（図3）においてバブル数のバラつきと
閉塞率による分布に一部規則性が認められなかっ
た。しかし、模擬血液流量と回転数から求め
た係数とバブルの関係（図5）においては、閉
塞率や送血管のサイズに関係なく統計学上
（p<0.05，Tukey-Kramer法）の有意差は認め
られなかった。しかし、唯一、係数と温度変化
の関係においては若干の有意差を認めた。

この理由として、著者らが行った臨床状態を
模擬した水系実験では、まず図3の閉塞率を変
化させたときに高い閉塞率で規則性が認められ
なかったことは、閉塞率80%では喙やかではあ
るが遠心ポンプへ模擬血液が送られるのに対
し、閉塞率100%では一時的に流れが遮断され
る。この間に細かい気泡は凝集しこうの大きな
バブルとなることでバブル数が減少したと考え
られた。また、バブル数にバラつきがみられた
のは、通常液体は、低温状態では粘性係数が大
きくなり相対的にキャビテーションが起こりやす
くなるという報告がある19)。このことからも
低温状態（10℃，20℃）においては、模擬血液
の粘性変化が大きく影響したと考えられた。
一方、各種条件が係数範囲に与える影響につ
いて、温度変化のみで差がみられる点に関して
も温度変化による粘性変化が原因と考えられ
た。そこで温度条件の中でも低体温（10℃，
20℃）を除いた、臨床に起こり得る条件
（30℃，36℃，37℃）のみ再度統計学的処理
（p<0.05，Tukey-Kramer法）を行ってみると
有意差は認められず係数が臨床使用上問題ない
ことが示された。

ここで、この係数を用いてPCPSにおけるキャ
ビテーション防止を目的とした観血表を作成
した。

1. 至適流量を求める観血表
ポンプ回転数（rpm）と係数（mL/rpm・
min）から至適流量を求める観血表を図6に
示す。これは、係数の中で最もバブル数が集中
した最大値0.8（赤色）、最小値1.4（黄色）
と実験中、各送血管の太さ（Fr）別のうち気泡
計測器にて1つでもバブルが認められた時の値
（青色）の3つの係数と回転数から理論値を求
め作図した。

（ただし、条件として非臨床的な条件を省い
t、血液流速温度30℃〜37℃、閉塞率0〜80%
以内の場合に限る。）

使用方法としては、回転数をもとに流量を見
た場合、赤色と黄色の直線で囲まれた範囲にあ
ればバブルの発生頻度が非常に高い状態であ
り、黄色を青色に囲まれた範囲にあればバブル
の発生が極めて低い危険領域となる。また、
青色の直線より上に行けば安全域になることが
容易に推定できる。

本研究で導き出された観血表は新規のデバ
イスを必要とせず、通常モニタリングされている
回転数と流量のコントロールによりキャビテ
ーションによる気泡発生を抑える可能性が
ある点で有用であると考えている。ただし遠心
ポンプの径により係数は変動するため、他の遠
心ポンプでは係数を測定しなおす必要がある。
また、今回はグリセリン水溶液を用いた水系実験であったため血液でも再現性が得られるか今後更なる検討が必要であると考える。

V. 結語
1. 臨床的な条件であればキャピテーションによる気泡発生とPCPSの設定条件の関連性は係数(L/rpm·min)を用いることで表すことが可能である。
2. 今回提案した早見表により、個々の患者の状態に合わせてキャピテーションによる気泡発生の危険性を予測することが可能である。
3. 実験は、水系実験のため今後さらなる検討が必要である。

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