Journal club Session 1 - What is research even?

Examining a Paper

Jia Yee, Sylvia, Winnie & Naveen
What do you expect in Introduction?

• Introduction should:
  ✓ provide a background to the study
  ✓ identify the need for the new research that is being presented
  ✓ provide a balance of related and recent literature

• Literature review
  ✓ a search and evaluation of the available literature in the given subject or chosen topic area

• how the work is intended to relate to others’ work?
• the problem that is being tackled and how?
• what knowledge and ideas have been established?
What do you expect in Introduction?

- Is the problem clearly identified?
- Is a rationale given for the research?
- Is the literature up to date?
- Is the literature relevant to the research?
- Does the literature present a balanced view?
- Does the literature identify a need for the research proposed?
The Stoplight Program: A Proactive Physical Therapy Intervention for Children With Acute Lymphoblastic Leukemia

Abstract
Chemotherapy may cause neuromuscular impairments that can have life-long effects. The Stoplight Program (SLP) was developed as a proactive physical therapy (PT) intervention directed at impairments in children with acute lymphoblastic leukemia (ALL). In this program evaluation, we assessed the feasibility of the SLP delivered as part of standard care and identified body function and activity patterns in patients who received the intervention. Children ages 1 to 22 years, diagnosed with ALL, received an assessment by a physical therapist as part of usual care. The SLP intervention used 3 levels to categorize the impairment levels and intensity of PT. Of the children (n = 135) screened, 46% completed 5 intervention visits and 32% completed the program and met discharge criteria. At initial assessment, 46% of children ages 1 to 5 years and 67% of children ages 6 to 22 years had abnormal motor function. Those completing the program tested within the healthy norms. Research is needed on variables that influence adherence to a PT program and the range of functional impairment and activity limitations in this population.
**The Stoplight Program: A Proactive Physical Therapy Intervention for Children With Acute Lymphoblastic Leukemia**

**Introduction**

Although chemotherapy treatment regimens for children and adolescents with acute lymphoblastic leukemia (ALL) are very effective, agents such as vincristine, dexamethasone, and intrathecal methotrexate can cause neuromuscular and skeletal impairments leading to lifelong challenges with physical function (Ness et al., 2012; Ness et al., 2015). An additional consideration is the impact of these neuromuscular and skeletal impairments on a developing child. Over the 2- to 3-year course of leukemia treatment, children need to advance in their motor development. Children have developmental work to do and taking a “time-out” can interfere with their ability to reach the norms of their healthy peers (Hooke, 2009; Lansky, 1985; Miles & Holditch-Davis, 2003). For example, young children need to learn how to run, skip, and hop, while receiving agents that can cause osteopenia (Mostoufi-Moab et al., 2012; Sala & Barr, 2007; Wasilewski-Masker et al., 2008), osteonecrosis (Kawedia et al., 2011; te Winkel et al., 2011), balance impairments (Wright, Galea, & Barr, 2005), muscle weakness (Gocha Marchese, Chiarello, & Lange, 2003; Hartman, van den Bos, Stijnen, & Pieters, 2008; Ness et al., 2013), peripheral neuropathy (Gilchrist & Tanner, 2013; Smith et al., 2013), and decreased ankle range of motion (ROM; Hartman, van den Bos, et al., 2008; Ness et al., 2012; Wright, Halton, Martin, & Barr, 1998). Motor performance impairments can persist into survivorship (Gocha Marchese et al., 2003; Hartman, van den Bos, et al., 2008; Ness et al., 2013), making participation in physical activity difficult and potentially augmenting cardiovascular risks (Wright et al., 1998). Therefore, it is imperative to explore early intervention to improve physical function and promote ongoing motor development, long-term health, and quality of life (Smith, Fisher, & Hamer, 2015).

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Physical therapy (PT) and physical activity intervention research is emerging in the pediatric oncology population. Studies have been small, focused on children with ALL, and have used time-limited supervised or home-based physical activity programs often addressing global impairments (Huang & Ness, 2011). Research outcomes demonstrated improved cardiopulmonary fitness, increased strength, and ROM, improved physical function, and decreased fatigue (Huang & Ness, 2011). The exercise intervention evidence in pediatric oncology has been rated at a low to mid-level with the majority of studies at the exploratory, descriptive, or pilot level (Baumann, Bloch, & Beulertz, 2013). Researchers demonstrated that interventions with ankle dorsiflexion stretching and lower extremity strengthening during treatment for ALL increased knee extension strength and ankle ROM but did not lead to a significant change in functional ambulation (Marchese, Chiarello, & Lange, 2004). Researchers also evaluated an intervention that addressed treatment-related impairments with a focus on hand/leg function, ankle ROM, and jumping, but found no difference between the intervention group and control group when comparing motor skills, ankle ROM, and bone density (Hartman et al., 2009). Poor adherence was discussed as the main reason for the limited treatment effect. These studies point to the need for an innovative intervention program tailored to the specific treatment-related impairments as well as the child’s developmental needs and time point in cancer treatment.
Materials and Methods

• Contain technical details on how the experiments were done.
• Should be detailed enough for another scientist to replicate the work.
• Always look out for these while reading
  ✓ Sample size (Is the sample size big enough? Is it randomised?)
  ✓ Repeats? (How many independent experiments were done?)
  ✓ Controls (Are there any controls to validate the results?)
  ✓ Ethics (Ethical approval needed for human research)

DOES THE METHOD USED ANSWER THE BIG QUESTION?
3. Research question

Are sirolimus-eluting PF stents associated with a higher, comparable, or lower incidence of MACEs at 1 year when compared with sirolimus-eluting stents with BP?

4. Methods

4.1. Study design

This is a prospective, open-labeled, single-center randomized controlled clinical trial. Inclusion criteria were patients between 18 and 80 years of age, with stable coronary artery disease or recent ACS (excluding those patients who were within 1 week of a STEMI [ST-elevation myocardial infarction]), who were being taken up for elective percutaneous coronary intervention. Exclusion criteria were patients with chronic renal failure, questionable drug compliance, expected survival of less than 1 year, significant peripheral vascular disease, those who refused informed consent, concomitant significant valvular heart disease, previous coronary revascularization procedure, previous cerebrovascular accident, known allergies or intolerance to antiplatelet agents, and patients requiring anticoagulation with vitamin K antagonists for any indication.

4.2. Randomization

Randomization protocol chosen was block randomization into groups of four. Based on the permutations, there would be 16 different recurring combinations. Fifty-one random blocks were chosen by a script written in python programming language.

4.3. Hardware

The stents chosen were Yukon Choice (PF) and Yukon Choice PC (BP). The hardware details are compared in Table 1.

4.4. Sample size calculation

Baseline values taken were from the ISAR TEST 3 trial as the trial was performed with the same two stents. The difference in MACE events in the aforementioned trial at 1 year was 9.5%, and the standard deviation was 0.24. Assuming null hypothesis, 80% power and 5% alpha error, to detect a difference of 10% between the two groups, the sample size was calculated to be 92 in each arm. To allow for 10% loss to follow-up, the sample size was calculated to be 204.

4.8. Ethical considerations

The study design was cleared by the institutional review board, and the trial was registered with the Clinical Trials Registry of India (CTRI) under CTRI/2013/03/004512. All patients were included in the study after obtaining an informed written consent.

4.9. Statistical analysis

Difference in the primary end point was evaluated using the chi-square test with values less than 0.05 taken as significant.
Original Article

Zerumbone targets the CXCR4-RhoA and PI3K-mTOR signaling axis to reduce motility and proliferation of oral cancer cells

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Materials and methods

Chemicals

Zerumbone was purchased from Sigma Aldrich, MO, USA with reported purity of \( \geq 98\% \) by HPLC analysis. Cisplatin and gefitinib were purchased from Selleckchem, TX, USA with reported purity > 99\% by HPLC analysis. All drugs were dissolved to 20 \( \mu \)M (zerumbone and gefitinib) in dimethyl sulfoxide (DMSO) and cisplatin in water and further diluted in culture medium for immediate use or stored in \(-20^\circ\)C.

Cell culture

The panel of OSCC lines (ORL series) used in this study were established from oral cancer patients as previously reported (Fadlullah et al., 2016; Hamid et al., 2009). All ORL cell lines were cultured in Dulbecco’s Modified Eagle’s Medium/Nutrient mixture F12-Ham’s medium (DMEM/F12, Hyclone, Utah, USA) supplemented with 10\% (v/v) of heat inactivated fetal bovine serum (FBS, Gibco, Auckland, NZ) and 500 ng/ml of hydrocortisone (Sigma-Aldrich, MO, USA). The primary oral keratinocytes (NOK; ORL 232 and ORL 235) used in this study were established from healthy gingival biopsies as previously reported (Hamid et al., 2009) and grown in Keratinocyte Serum-Free Medium (KSFM, Gibco, Auckland, NZ) supplemented with 25 \( \mu \)g/ml bovine pituitary extract (BPE), 0.4 ng/ml epidermal growth factor (EGF) and 0.09 mM calcium chloride (CaCl\textsubscript{2}). HCT-116 and MCF-7 were grown in DMEM (Gibco, Auckland, NZ) supplemented with 10\% (v/v) FBS. All cell lines have been authenticated as described previously (Fadlullah et al., 2016). Cells were cultured at 37\%C in a 5\% CO\textsubscript{2} humidified atmosphere.

Statistical analyses

All data are expressed as mean \pm SD from three independent experiments. The significance of differences between groups in each experiment was analysed by Student’s t-tests using GraphPad Prism software (GraphPad Software Inc., CA, USA). Differences were considered statistically significant at \( p < .05 \).
Results

☑ Found in original research paper
☒ Not found in review paper

What would you expect in results?
☑ Present the findings clearly & consistently, in line with the stated aim of the research.
☑ Make correct data interpretation, in line with findings presented.
☑ Results are not commented at this stage (describe BUT do not discuss)
☑ Make use of visual methods e.g. graphs / tables / images & provide sufficient detail for figure / table
☑ No gaps in the results
Expression levels of a filament-specific transcriptional regulator are sufficient to determine Candida albicans morphology and virulence

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Results

High-Level Constitutive UME6 Expression Is Sufficient to Promote Virulence in a Mouse Model of Systemic Candidiasis. One advantage of the tetracycline-regulatable gene expression system described above is that it can be used to control gene expression during infection in a mouse model of systemic candidiasis by the addition or removal of Dox in the drinking water (12, 14). To determine the effect of constitutive high-level UME6 expression on virulence, 16 mice were each injected with the tetO-UME6 strain. Three days prior to infection, 8 of these mice were placed on drinking water containing Dox; the remaining 8 mice were placed on drinking water lacking Dox. Strikingly, we found that whereas only 5 mice placed on drinking water with Dox died after 30 days, nearly all of the mice on drinking water lacking Dox died by 11 days post-infection (Fig. 3A). We also observed that virulence of a control strain that lacks the tet operator is not affected by the presence or absence of Dox (data not shown). These results strongly suggest that constitutive high-level UME6 expression promotes virulence in a mouse model of systemic candidiasis. It is important to note that increased virulence is observed relative to that of the tetO-UME6 strain in the presence of Dox, which expresses one functional copy of UME6. However, we have previously demonstrated that a strain expressing one functional copy of UME6 does not show a significant difference in virulence when compared with a WT strain (13).
Discussion

✓ The major findings of a study
✓ The meaning of those findings
✓ How these findings relate to what others have done

✓ Limitations of the findings
✓ An explanation for any surprising, unexpected, or inconclusive results

✓ Suggestions for further research
✓ The “take away” message.
Major findings

How this findings relate to others’

Strength

The Stoplight Program: A Proactive Physical Therapy Intervention for Children With Acute Lymphoblastic Leukemia

Discussion

The development of the SLP with its performance measurements provides insight into the feasibility, outcomes, and barriers to implementation of PT intervention for children with ALL across a large medical system. It also informs us about the rehabilitation needs of this patient group and patterns of physical performance while patients are receiving both treatment for ALL and the proactive PT intervention. First and foremost, the results demonstrate that PT is needed by children with ALL and the SLP is a feasible method for administering a PT intervention. Approximately one third of our participants were able to complete the program with goals met. However, there were a number of children in the other groups who did receive several PT visits prior to being discharged to PT in their community or deemed unable to adhere to the program.

Previous studies investigating PT interventions have been successful in administering an intervention in children with ALL. In their study of 17 ALL patients enrolled in a 6-month home-based exercise program, Esbenshade et al. (2014) reported that 71% of patients completed the study. Intervention outcomes were defined by the percentage of who experienced greater than a 5% improvement in function. Eighty-two percent had an improvement

In contrast to these controlled research studies with specifically timed interventions in the maintenance phase of ALL, the SLP was implemented as a standard of care across an entire diagnostic population beginning at diagnosis, and continuing until patients met discharge criteria. This approach avoided selection bias that can occur with recruiting only “motivated” participants to a research study but could also explain why retention rates were lower than published pilot studies (Esbenshade et al., 2014; Marchese et al., 2004).
Weakness

The Stoplight Program: A Proactive Physical Therapy Intervention for Children With Acute Lymphoblastic Leukemia

had taken place. Reasons for nonadherence to the SLP were not directly explored with families. In a study of adherence to adult cardiac rehabilitation, travel was found as the most common cited barrier (Shanmugasigaram, Oh, Reid, McCumber, & Grace, 2013). Little is known about adherence to PT in the pediatric population and more research is needed. In children with cancer, research on adherence is focused on oral chemotherapy and is defined as a complex, multidimensional behavior involving active self-care steps through collaboration with the health care provider (Landier, 2011). When adherence

A limitation of this evaluation was the use of a descriptive design to summarize the outcomes of the patients in the SLP. While using a formal research approach, such as a randomized clinical trial, would provide a higher level of evidence, we sought to focus on the implementation and evaluation of a tailored intervention program implemented as a standard of care and imbedded in real-world clinical practice. Future research should include the actual ankle ROM results versus a categorical measurement as consistent with previous studies in children with ALL. An additional limitation was the lack of outcome

Reasoning, support with others’ work