温泉利用による健康教育のＲＣＴ

シンポジウム
学際領域における評価のデザイン
－RCTとシステマティック・レビュー－の現状－
2006.2.18(土), 東京大学

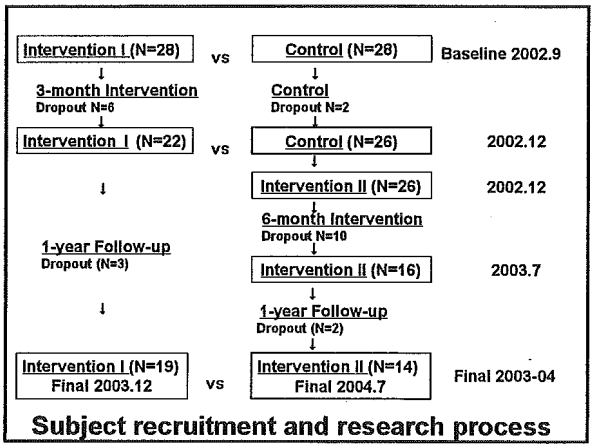
東京農業大学地域環境科学部教養分野
上 岡 洋 晴

中高年女性を対象とした温泉入浴と生活・運動指導による総合的健康教育

- 3ヶ月間と6ヶ月間介入の無作為化比較試験の1年後追跡 -

○上岡 洋晴 （東京農業大学地域環境科学部教養分野）
岡田 真平・高橋 美絵（身体教育医学研究所）
中村 好一（自治医科大学公衆衛生学教室）
上馬場 和夫（富山県国際伝統医学センター）
矢崎 俊樹（日本健康開発財団）
武藤 芳照（東京大学大学院身体教育学講座）

(J Epidemiol, 16(1): 35-44, 2006)



Subject recruitment and research process

総合的健康教育プログラム

生活・運動指導 60分	＋	温泉入浴指導 60分(更衣, 洗身含)

- ストレッチング
- ウォーキング
- 水中運動

- 調理実習
- スポンジテニス
- リズム運動

- 栄養価計算 など

- ナトリウム塩化物泉
- 露天浴槽, 41.5℃

指導スタッフ:
温泉入浴指導員2名
健康運動指導士, 理学療法士,
保健師, 栄養士

（すべての写真は修正なしでの公表を了承済）

調査・測定項目

- 体格:
  身長, 体重, Body Mass Index
- 血液性状:
  総コレステロール, HDLコレステロール,
  動脈硬化指数, 尿酸, ヘモグロビンA1c
- 有酸素性作業能力:
  自転車エルゴメータによるPWC$_{75\%HRmax}$
- 膝・腰の疼痛度:
  Visual Analogue Scale
- 精神心理状況:
  日本語版POMS, 自己評価式抑うつ尺度,
  主観的幸福度(VAS)

結果のまとめ

- 週1回、2時間で、3ヶ月間の介入では、直後に気分や有酸素性作業能力、血液性状、腰痛の改善に効果が見られたが、追跡1年後までは維持できなかった
- 同じ内容のプログラムで、週1回、2時間で、6ヶ月間の介入では、終了後1年後まで、有酸素性作業能力、HbA1c、腰痛、活気、抑うつ、疲労などが有意に改善・向上したままであった

温泉の治療と健康増進効果に関するRCTのシステマティック・レビュー

○上岡 洋晴(東京農業大学地域環境科学部教養分野)
岡田 真平, 高橋 美絵(身体教育医学研究所)
小松 泰喜(東京厚生年金病院リハビリテーション科)
矢崎 俊樹(日本健康開発財団)
上馬場 和夫(富山県国際伝統医学センター)
津谷 喜一郎(東京大学大学院医薬経済学講座)

(日本温泉気候物理医学会誌, 69(3):印刷中, 2006)

「温泉」に関するRCT先行研究レビュー

<適格基準>	
1. キーワード	「spa」「balneotherapy」
2. データベース	Pub Med
3. 研究デザイン	RCTによる研究
4. 出版の時期	1990年以降
5. 言語	英語
6. 複数発表	新しい方の論文結果を記載
7. サンプル数・観察期間	制限なし
8. 対象	制限なし
9. 検索日	2005年4月

RCTの研究の質を評価するPEDro scale改変版

1. ランダムなグループ分けがなされたか？
2. 群の割付方法は割付時に隠蔽されたか？
3. 介入群と対照群はベースラインで同等だったか？
4. 対象者は盲検化されたか？
5. 治療者は盲検化されたか？
6. 評価者は盲検化されたか？
7. 少なくとも主要な1指標において最初の対象者の85%以上の測定がなされたか？
8. 少なくとも主要な1指標においてITT分析がなされているか？
9. 少なくとも主要な1指標において統計学的な群間比較がなされているか？
10. 少なくとも主要な1指標において点推定と信頼区間が示してあるか？

11. 十分なサンプル数があるか？(ベースラインで各群ともに50以上)
12. 十分なフォローアップの期間があるか？(3ヶ月以上)
13. 温泉の成分別の割付をしたか？(複数の泉質間の比較)

Q.1-10はPEDro scale, Q. 11-13は追加項目.13点満点.

疾病に対する温泉療法の17研究

対象とした疾患等	研究数
リウマチ性疾患	6
(リウマチ＋外傷の後遺症)	(1)
(リウマチ＋変形性関節症)	(1)
変形性関節症	4
(変形性関節症＋腰痛)	(1)
腰痛症	3
パーキンソン病	1
静脈瘤	1
乾癬	1
健康増進	1
泉質の差異を検討した研究	8
研究を実施した国	
フランス	7
ドイツ	3
イスラエル	3
オランダ	2
イタリア	1
日本	1
研究の質の評価*	7.5±2.3 (2-12)

* mean±SD (min - max)

リウマチ患者を対象にした研究

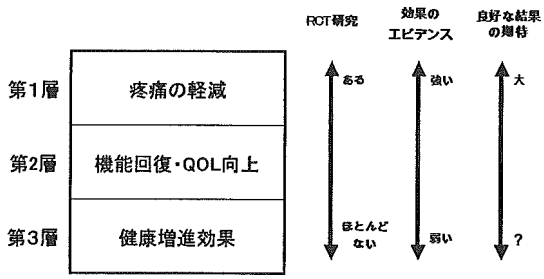
報告者(報告年)	Franke (2000)	Van Tubergen (2001, 2002)	Elkayam (1991)	Sukenik (1995)	Allard (1998)
観察期間	6ヶ月	11ヶ月	6ヶ月	9ヶ月	12ヶ月
スコア	12	10	7	5	2

腰痛患者を対象にした研究

報告者(報告年)	Constant (1999)	Constant (1995)	Guillemin (1994)
観察期間	3ヶ月	6ヶ月	9ヶ月
スコア	9	8	7

その他の疾患患者等を対象にした研究

報告者(報告年)	Brefel-Courbon (2003)	Mancini (2003)	Gambichler (2001)	Kamioka (2004)
観察期間	5ヶ月	6ヶ月	7.5週	6ヶ月
スコア	8	7	7	5



温泉医学の確立すべきエビデンス3層モデル
(上岡ら:日本温泉気候物理医学会誌,69巻3号,2006)

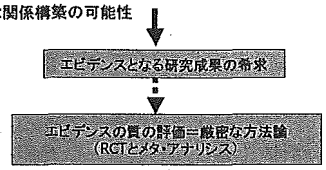
教育学分野でのシステマティック・レビュー
ー教育学でのエビデンスの産出ー

シンポジウム
学際領域における評価のデザイン
ーRCTとシステマティック・レビューの現状ー
2006.2.18(土), 東京大学

国立教育政策研究所生涯学習政策研究部
岩崎久美子

1はじめに:アウトライン
1−1 研究と政策の対話:官庁附属研究所の位置づけ

- ・"政策に役に立つ研究":需要中心ではない供給優位の現実
- ・説明責任(アカウンタビリティ)としての研究評価
- ・理性的な関係構築の可能性



1−2 研究・研究成果のマネージメント:研究による知見(知識)創出、成果普及、評価

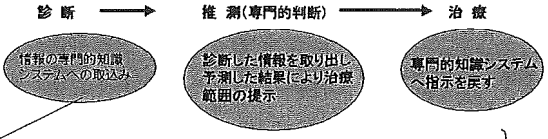
- 生産された研究を集約し、そこからどのように知見を導くか
  (viz. どのように"政策に役に立つ研究" にするか)

研究・研究成果のマネージメントの問題

【ex.ショックレー博士の失敗】
:優秀な科学者が優秀な経営者ではないという事例
- トランジスタの発明者として「トランジスタの父」と呼ばれ、ジョン・バーディン、ウォルター・ブラッテンらとともにノーベル物理学賞(1956年)受賞
- 1955年にショックレー半導体研究所をパロアルトに設立、優れた英才を集めたが、その中のロバート・ノイス(後にインテルを設立)ら8人がショックレーのやり方に不満を持ち退職、フェアチャイルド社を設立、後のシリコンバレー発展のひとつの契機となる

2医学・薬学と教育学の共通点・相違点(医師と教師)
2−1 共通点

- クライアントの問題を診断し解決策を分析(推測)・分類(治療)
- 医者と患者(教師と子ども)との間の知識量の差を前提



●知識の結合(知識の総動員)colligation⇒有効な根拠と判断する一連の規則
Ex.病気の種類の特定・学習困難の要因特定⇒問題の適切さ、選択決定
●分類classification⇒正当な証拠を専門的に並べ診断名を付与

(Hargreaves, D.H. 2000)

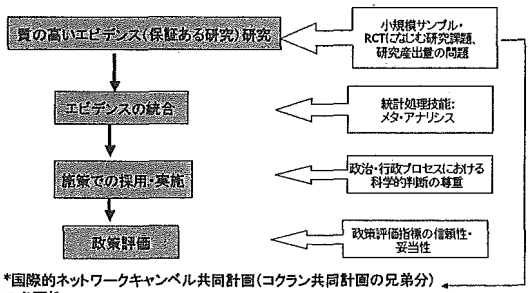
2−2 医師と教師の知識ベースの差異

	医 師	教 師
知識の活用	・コアになる知識ベース ⇒幅広い臨床経験 ⇒コアになる知識ベース(新しい知識)	・コアになる知識ベース ⇒幅広い経験⇒経験を解釈するために知識ベースを利用
対象	・患者個人	・クラス全体
治療(対応)の根拠	・生物医学的科学(biomedical sciences)に根拠:科学的根拠	・直感的・独創的 ・個人的パーソナリティ 社会科学を根拠とできるか? ⇒心理学・社会学(理論・概念)での知識ベース!
判断根拠	・専門家の重要な特徴である難解な知識ベース(Larson, 1977)	・担当教科に関する知識(教科課程の修了による知識)、教授スキルは経験から獲得
知識創出の場	・病院(実践者と研究者)	・学校(現場)と大学の乖離

- ・社会的ステータスの差異=知識創出(knowledge creation)・普及(dissemination)の差異

(Hargreaves, D.H. 2000)

3エビデンス産出プロセスと課題



*国際的ネットワークキャンベル共同計画(コクラン共同計画の兄弟分)の必要性

4教育学でのRCTs/SR事例

4－1 米国でのランダム(無作為)試験(RCTs)研究例

独立変数	従属変数
●放課後プログラム導入 →	数学の成績と読解力の向上
●保護者の育児能力向上プログラム導入 →	就学前の児童の無秩序行動の抑制 (3ヶ月から24ヶ月までの子ども)
●サマースクール (学校層の変更) →	階層間(低所得階層の長期夏期休暇での学力低下)学力格差を減少
●学級サイズの変更 (24～26人に条件設定) →	学力向上 テネシー州長期調査(STAR):幼稚園から3年生までの児童を対象

4－2 キャンベル共同計画に見るSR

- ●司法精神サービスで精神障害と診断された人の暴力行動を防止するための介入
- ●小学校でのピア・サポートによる学習
- ●ボランティア個人教授プログラムの効果に関するエビデンス
- ●小学生の成績向上への親の関与の効果
- ●社会情報処理スキルの向上を目的とする校内介入が攻撃行動に与える効果・高校中退の防止
- ●放課後プログラムが生徒のアウトカムに与えるインパクトのシステマティック・レビューのためのプロトコル
- ●すべての医療職種の学生・研修生の職務上の成果に対するオンラインの情報入手技術へのアクセスの効果
- ●就学前児童の認知・情緒面のアウトカムに対するセサミストリート番組の効果

↓

教育の臨床・病理領域(特別な教育ニーズ・矯正教育)の近似性

5エビデンス産出の方向性

5－1 研究上の問題

- 介入効果が明快な学力向上・問題行動・矯正教育などの特定領域に限定 (バイアスの問題)
- 研究実施上の倫理上の問題(人間を対象にする実験計画)
- 実験計画の依頼先(附属学校で可能か？)
- 「RCT⇒メタ・アナリシス」ではない研究手法の代替性:大規模社会調査

ex. 社会階層と移動に関する全国調査(SSM調査)・米国High School and Beyond(高校生対象の大規模追跡調査)などの先行研究の妥当性検証の追試など

5－2 エビデンスをもたらす研究への政策志向・誘導

- 根拠あるデータで政策の妥当性を国民に説明する道義的義務 ・社会認識の高まり
- 実証性に基づかない施策の経費浪費(無駄遣い) (費用対効果・政策効率の問題)
- 意見に基づく政策(opinion-based Policy)の限界

→ ・知識伝達やコミュニケーションスタイルの変化
・政策決定システムの透明性志向

5－3 米国の社会科学の政策志向

- 厳密な手続きを経た実証を伴う数量研究への政策要求

"教育学は学問上の流行に翻弄されることなく科学的根拠ある研究に転換するという文化的変容が求められる"
(U.S. Department of Education, Strategic Plan 2002-2007).

- 米国教育省助成研究への質の評価
  第三者評価機関決定(2007年まで全体の95%)
  ランダム(無作為)試験(RCTs)採用(2007年まで全体の75%) ⇒政策誘導

・科学的手法を使った研究成果を教育施策に反映
・レビューに値するランダム(無作為)試験(RCTs)による研究成果の産出を促進

ex:キャンベル共同計画と米国教育研究所(American Institutes for Research):
アメリカ連邦教育省情報センター(What Works Clearinghouse)「文献検索ハンドブック」(Literature Search Strategy Handbook, May 29,2003.)

5－4 政策科学としての教育学

- 研究手法の厳密な質の保証とその成果活用
- 社会的ニーズに基づく厳密な研究手続きを経た質の高い研究成果の産出・社会的活用
- 社会科学に基づく専門的知識ベースの確立 ⇒教員教育への適用
- 政策科学研究としての科学的手法の採用

司法領域のRCTとSR

静岡県立大学
津 富 宏

エビデンスに基づく社会へ

- 実験する社会　から
  - Experimenting Society
  - Donald T. Campbell
- エビデンスに基づく社会　へ
  - Evidence-Based Society
  - 実現は、医学において先行
    - EBM: Evidence-Based Medicine
    - コクラン共同計画
  - 行政改革の動きと連動し、政策全般へ

一次研究と二次研究の役割分担（やや強引に）

一次研究	内的妥当性の担保
二次研究	外的妥当性の担保
	統計的結論妥当性の担保
	（二次レベルでの）構成概念妥当性の担保

刑事司法におけるRCT

- Palmer and Petrosino, 2003
  - 700件あまり
- Farrington, 1983; Farrington and Welsh, 2005
  - ①最低50単位が実験群あるいは統制群に割り付けられた、②犯罪をアウトカムとしている、③英語で発表されたRCT
    - 1957年から1981年の間に35件
    - 1982年から2004年の間に83件

刑事司法におけるRCTの例

- Cambridge-Summerville experiment（McCord, 1978）
  - おそらくアメリカで最初のRCT
  - 介入：男子非行少年に対する「暖かな指導、社会的サポート、放課後の活動、必要に応じ個別学習指導・医療
  - 1930年代に始まる縦断的研究、1970年代まで追跡
    - 長期追跡によって、下記の知見が明らかとなった
  - 統制群に比べ、実験群は
    - 重大街路犯罪で有罪起訴を受けやすい
    - 約5歳早く死亡した
    - アルコール中毒、統合失調症、躁鬱の診断を受けやすい
  - もっとも明瞭に、プログラムの有害性（criminogenic effect）を示した実験

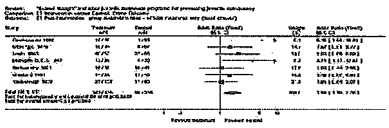
刑事司法におけるSR

- 必ずしもRCTを対象としない
- Petrosino and Soydan (2005)
  - 犯罪者処遇について50件のSRがある

ブートキャンプ	1	暴力犯罪	1
認知行動療法	2	処遇全般	4
薬物犯罪・飲酒運転	3	刑務所における作業教育	1
「実験」	1	刑罰	2
ヨーロッパ	3	リラプス防止	1
家族に基づく介入	4	修復的司法	1
女性犯罪者	1	性犯罪	6
非行少年	19	合計	50

刑事司法におけるSRの例

- Petrosino, Turpin-Petrosino, and Buehler 2003. 'Scared Straight' and Other Juvenile Awareness Programs for Preventing Juvenile Delinquency. Campbell Review
  - 7件のRCTを統合
  - 効果値=1.68 (95%信頼区間 1.20, 2.36) 有害



キャンベル共同計画

- 社会政策における系統的レビューの成果を提供する唯一の国際的プロジェクト
- 部会
  - 方法論部会
    - キャンベル・ガイドラインを作成(キャンベルレビューの品質管理)
  - 広報・コミュニケーション部会
- 主要3領域
  - 教育部会
  - 刑事司法部会
    - http://www.aic.gov.au/campbellcj/
  - 社会福祉部会

エビデンスの活用 とりわけ、犯罪者処遇において

- 二つの手法がある。
  1. Model Programs を確定して普及
     - 特定のプログラムについて、RCTやSRによって効果検証を行う。
     - どちらかというと、一次研究をベースにする発想
  2. 有効な処遇のelementsを確定して普及
     - 処遇全般に関するSRを行い、有効な処遇の本質を抽出する
     - SR、とりわけ、メタ回帰分析をベースにする発想

Model Programs を普及する

- Blueprints for Violence Prevention
- http://www.colorado.edu/cspv/blueprints/model/overview.html
- コロラド大学が運営。司法省少年司法非行防止局による支援。
- 目的1 Model Programの認定
- 目的2 Model Programの普及

有効さのelementsの普及

- Howell and Lipsey (2004)
  - 4つのelements
    - 主たるサービス
    - 従たるサービス
    - サービスの実施(密度、期間など)
    - 対象者とのマッチング

エビデンスを行政へ

- 政治を通じて
  - 費用効果分析: Washington State Institute for Public Policy
    - Aos et al. (2004) 非行予防・処遇プログラム
  - メディア報道: ウェブサイトは政策転換を生み出さない
- 行政へ
  - エビデンスを欠くプログラムへの予算配布の中止
  - 実施品質の管理

国際援助の評価

シンポジウム
学際領域における評価のデザイン
－RCTとシステマティック・レビューの現状－
2006.2.18(土), 東京大学

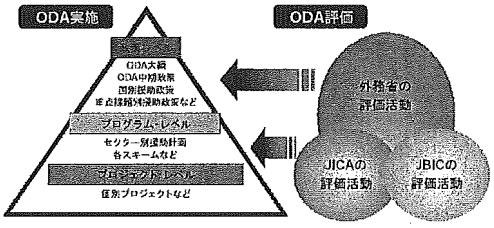
国際医療福祉大学大学院保健医療学専攻
正木朋也

日本の政府開発援助(ODA)評価

- 1954　政府開発援助(ODA)開始
  - 各プロジェクトの事後評価中心(案件管理)
- 1975　説明責任の重要性(OECD DAC)
  - 外務省と実施機関(JICA, JBIC)
- 1990～　援助疲れ、国民へのフィードバック
  - 中間、事前評価(案件実施の妥当性)
- 1998　ODA評価連絡会議(関連府省)
- 2000　日本評価学会設立
- 2000～　評価の多様化(合同評価)
  - プロジェクト → セクター、国別、事業別
  - 評価の透明性(第三者評価)
  - Results Based Management の可能性

2

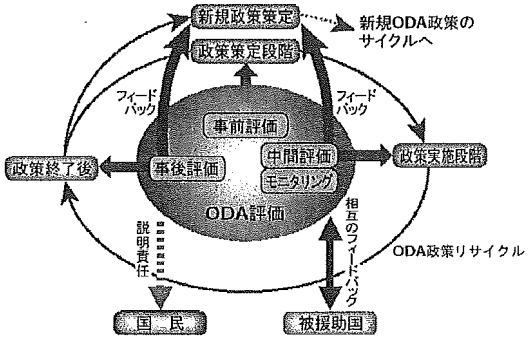
評価の実施体制と評価対象



経済協力評価報告書 第一章2004 ODA評価の歩み(p.12)

3

ODA評価の機能



経済協力評価報告書 第一章2004 ODA評価の歩み(p.14)

4

Results Based Management (RBC)

- 組織活動を業績と結果から管理
- 目標、測定指標の設定
- 定期的モニタリング
- 必要に応じた評価
- インプットよりもアウトプット、アウトカム

＜背景＞
ゴア米国副大統領の報告書:
National Performance Review(1993)
政府業績成果法(GPRA):
Government Performance and Results Act, 1993)

5

日本の人文・社会学領域における RCT/SRの普及

- 日本評価学会(2000年9月設立)
  - 国内外の公共投資を適切に評価すること
- 社会実験分科会の活動
  - 社会実験分科会セッション(2002.12開催)
  - 先行事例等紹介
    コクラン共同計画、キャンベル共同計画、What Works Clearinghouse(WWC)、貧困アクションラボ
  - 日本評価研究特集号(2006年3月出版予定)

6

国際援助におけるRCT日本語論文

医学中央雑誌検索：1件

- 中西由季子, 発展途上国における鉄欠乏症撲滅活動ーとくにベトナムをモデルケースとしてー 報告その3: 大規模介入試験の成果. イルシー;2005;81:69-72.

7

貧困アクションラボ
Poverty Action Lab

- インド 8件
- インドネシア 2件
- フィリピン 2件
- ケニア 15件
- 南アフリカ 2件
- マダガスカル 1件
- ペルー 2件
- コロンビア 2件

- 他、アメリカ国内で実施の8件を加えた計42件
- 教育(主に初等教育)、保健、ジェンダー、マイクロクレジット、地方分権化
- ホームページ、定期購読誌による広報

8

人文・社会科学領域における
RCT/SR普及の壁

- 量的研究と質的研究の対峙
  - パラダイム論争(対象把握法の違い)
- RCT信奉者らによる誤解の普及
  - エビデンスにはレベルがあることの周知
- Evidence-based への批判
  - RCT-based であろうとの誤解の払拭
- システマティックレビューの重要性無理解
  - 介入研究の質評価プロセスの周知

9

RCT/SR普及のために

- エビデンスにはレベルがあることを知る
- エビデンス利用者(受益者)の価値基準、好み、現場の状態を含めた判断に役立つ
- 既存の評価判断に齟齬を来たすものではなく、むしろ相補的に役立つ
- 介入のみならず、診断・予後などについてのエビデンスも産出可能
- 多くの領域でエビデンスを蓄積し、正しく利用することの社会・公共的価値

10

RCT/SR今後の展望

- 保健医療以外の領域におけるエビデンスの蓄積
- 出版バイアス対策(例、臨床試験登録)
- 質的研究の質評価(質的研究のSR)
- 定量的・定性的アプローチの合成
- エビデンスに関わる知識伝播と社会認識
  - エビデンスの質とお勧め度のグレーディング
  - 場に適したメディアや手法による伝達

11

Thank you ...

Think globally, act locally
by Rene Dubos
Doing the right things right
by J.A. Muir Gray

Tomoya MASAKI
masakit-tky@umin.ac.jp

12

II. 研究成果の刊行に関する一覧表

雑誌

著者指名、論文タイトル、発表誌名、出版年、巻号、ページ。
1) Hirayama A, Kodama K, Yui Y, Nonogi H, Sumiyoshi T, Origasa H, Hosoda H, Kawai C: Effect of trapidil on cardiovascular events in patients with coronary artery disease. *Am J Cardiol* 2003; **92**: 789-793.
2) Yokoyama A, Origasa H, for the JELIS Investigators: Effects of eicosapentanenoic acid on cardiovascular events in Japanese patients with hypercholesterolemia: Rationale, design, and baseline characteristics of the Japan EPA Lipid Intervention Study (JELIS). *Am Heart J* 2003; **146**: 13-20.
3) Teramukai S, Matsuyama Y.: Exploring between study heterogeneity in individual patient data meta-analysis. *Controlled Clinical Trials* 2003; **24**: 113S-114S.
4) Watanabe, M, Yamaoka K, Yokotsuka M, Tango T.. Randomized controlled trial of a new dietary education program to prevent type 2 diabetes in a high-risk group of Japanese male workers, *Diabetes Care* 2003 ; **26** : 3209-3214.
5) Hashiguchi M, Ohno K, Kishino S, Mochizuki M, Shiga T, Comparison of cilostazol and ticlopidine coadministered with aspirin for long-term efficacy and safety after coronary stenting; a meta-analysis. *Jpn J Clin Pharmacol Ther* 2005; 36(2).
6) Origasa H, Ikeda Y, Shimada K, Shigematsu H: Oral beraprost sodium as a prostaglandinI2 analogue for vascular events in patients with peripheral arterial disease: meta-analysis of two placebo- controlled randomized trials. *Jap J Pharmacoepidemiol*, 2004; **9**(2): 45-51.
7) Shimada S, Yokoyama N, Origasa H, Tsuneki H, Kimura I: Progressive bone loss due to androgen deprivation therapy for prostate cancer: a meta-analysis. *Jpn J Pharm Health Care Sci*, 2005; **31**(3): 203-210.
8) 田崎美弥子, 石井八重子, 海老原良典, 折笠秀樹, 高山美智代, 広瀬信義, 角間辰之, 加藤芳朗, 国吉緑, LeeJung Won, 鈴木千智, 長谷川恵美子, 藤井美和, 畑田けい子, 松田正巳, WHOQOL-OLD調査票日本語版開発グループ:高齢者のQuality of Life(QOL)調査票開発プロジェクトにおける予備調査結果. 老年精神医学雑誌, 2005; **16**(2): 221-227.
9) Hirashima Y, Hamada H, Kurimoto M, Origasa H, Endo S: Decrease in platelet count is an independent risk factor for symptomatic vaso spasm following aneurismal subarachnoid hemo rrhage. *J Neurosurg*, 2005; **102**: 882-887.
10) Gotoh M, Kamihira O, Kinukawa T, Ono Y, Ohshima S, Origasa H, on behalf of the Tokai Urological Clinical Trial Group: Comparison of α1a-selective adrenoceptor antagonist, tamsulosin, and α1d-selective adrenoceptor antagnonist, naftopidil, for efficacy and safety in the treatment of benign prostatic hyperplasia; a randomized controlled trial. *Br J Urol Int*, 2005; **96**: 581-586.

11) Shikata S, Yamagishi H, Taji Y, Shimada T, Noguchi Y. Single- versus two- layer intes tinal anastomosis: a meta-analysis of rando mized controlled trials. *BMC Surg.* Jan 27,2006; 6(1):2.
12) Hayashino Y, Goto M, Noguchi Y, Fukui T. Ventilation-Perfusion Scanning and Helical CT in Suspected Pulmonary Embolism: Meta-Analysis of Diagnostic Performance. *Radiology.* Mar 2005; 234(3):740-748.
13) Hayashino Y, Noguchi Y, Fukui T. Systematic evaluation and comparison of statistical tests for publication bias. *J Epidemiol.* Nov 2005; 15(6):235-243.
14) Noguchi Y, Nagata-Kobayashi S, Stahl JE, Wong JB. A meta-analytic comparison of echocardiographic stressors. *Int J Cardiovasc Imaging.* Apr 2005; 21(2-3):189-207.
15) Shikata S, Noguchi Y, Fukui T. Early Versus Delayed Cholecystectomy for Acute Cholecystitis: A Meta-analysis of Randomized *Controlled Trials. Surg Today.* 2005; 35(7):553-560.
16) Yamaoka K, Tango T. Efficacy of Lifestyle Education to Prevent Type 2 Diabetes: A meta-analysis of randomized controlled trials. *Diabetes Care,* 2005; 28: 2780-6.
17) Ogata H, Furukawa C, Kawakami Y and Magae J. A Quantitative model for the evaluation of dose rates effects following exposure to low-dose gamma-radiation. *Radioprotection* 2005; 40, 191-202.

III. 研究成果の刊行物・別刷り

（主要な文献）

● Original Article

Oral Beraprost Sodium as a Prostaglandin I_2 Analogue for Vascular Events in Patients with Peripheral Arterial Disease : Meta-Analysis of Two Placebo-Controlled Randomized Trials

Hideki ORIGASA*1, Yasuo IKEDA*2,
Kazuyuki SHIMADA*3, Hiroshi SHIGEMATSU*4

〈Abstract〉
Objective : To evaluate the effect of beraprost sodium (beraprost) on the vascular events occurring in patients with peripheral arterial disease (PAD) in a meta-analysis of placebo-controlled, randomized trials.
Design : Meta-analysis
Methods : Among the clinical trials of beraprost in patients with intermittent claudication associated with PAD, placebo-controlled, randomized trials with vascular events as outcome measures were selected. Two trials met the criteria, each of which was a comparative trial of beraprost (40 μg t.i.d.) and placebo (t.i.d.), with a six-month follow-up period.
Results : With both trials combined, the analysis included 594 patients in the beraprost group and 590 in the placebo group. The risk ratio was 0.608 (95%CI : 0.41 to 0.90, p=0.012), demonstrating the efficacy of beraprost on all vascular events. The risk ratio for lower limb deterioration was 0.598 (95% CI : 0.34 to 1.06, p=0.079), which was similar to that for all vascular events. A statistically insignificant but similar result was also obtained for cardio/cerebrovascular events with a risk ratio of 0.619 (95%CI : 0.36 to 1.07, p=0.085). Heterogeneity between the two studies was not found for any of the events.
Conclusion : The results demonstrated the efficacy of beraprost on the vascular events in patients with PAD. The potential benefit of beraprost on vascular events will require evaluation in a larger prospective investigation.

Key words : prostacyclin, beraprost sodium, meta-analysis, intermittent claudication, vascular event

Introduction

Beraprost sodium (beraprost) is an orally active prostaglandin I_2 (PGI_2) analogue, with antiplatelet[1], and vasodilating properties[2] and improvement of endothelial function[3]. Beraprost was launched in the Japanese market in 1992 and is currently marketed in 3 Asian counties to treat ischemic symptoms in chronic arterial occlusion and primary pulmonary

*1 Division of Biostatistics, Faculty of Medicine, Toyama Medical and Pharmaceutical University, Japan
*2 Division of Hematology, Department of Internal Medicine, Keio University School of Medicine, Japan
*3 Department of Cardiology, Jichi Medical School, Japan
*4 Department of Surgery, Faculty of Medicine, the University of Tokyo, Japan
Address for correspondence : Hideki ORIGASA, Faculty of Medicine, Toyama Medical and Pharmaceutical University, 2630 Sugitani, Toyama 930-0194, Japan

hypertension.

Ilprost is also known to be a PGI_2 analogue. It is administered intravascularly (iv) and is targeted for more severe (Fontane stages III and IV) patients. The efficacy of ilprost has also been demonstrated by a meta-analysis[4]. Therefore, this study is limited to the efficacy of beraprost for more mild (Fontane stages II) patients.

Although PGI_2 analogues were expected to be clinically applied in various ways due to their physiological activities[5,6], there are only a few reported placebo-controlled double-blind trials with PAD as the target disease to demonstrate efficacy in the treatment of arteriosclerotic disease[7]. Likewise, all reported trials of beraprost have only targeted PAD among arteriosclerotic diseases.

For beraprost, there have been four reported placebo-controlled, randomized, double-blind trials in patients with intermittent claudication (IC) due to PAD[8-11]. Of these four, two phase 3 trials[10,11] had claudication and cardiovascular events as outcome measures. A BERCI-2 trial[10] conducted in France and Italy demonstrated a significant improvement in claudication, while a study conducted in the United States[11] showed no statistically significant difference. Noteworthy was that the drug's tendency to improve cardiovascular events was observed in both studies ; however, a statistically significant difference was absent, which indicates that beraprost has not been fully proved to be effective for cardio/cerebrovascular events including myocardial infarction, cardiovascular death, and stroke as endpoints.

A meta-analysis of the two phase 3 trials was performed to evaluate the effect of beraprost on vascular events in more than 1,000 patients. The present meta-analysis not only assesses the value of beraprost in reducing vascular events but also provides important information for conducting clinical trials with cardio/cerebrovascular events as a primary outcome measure.

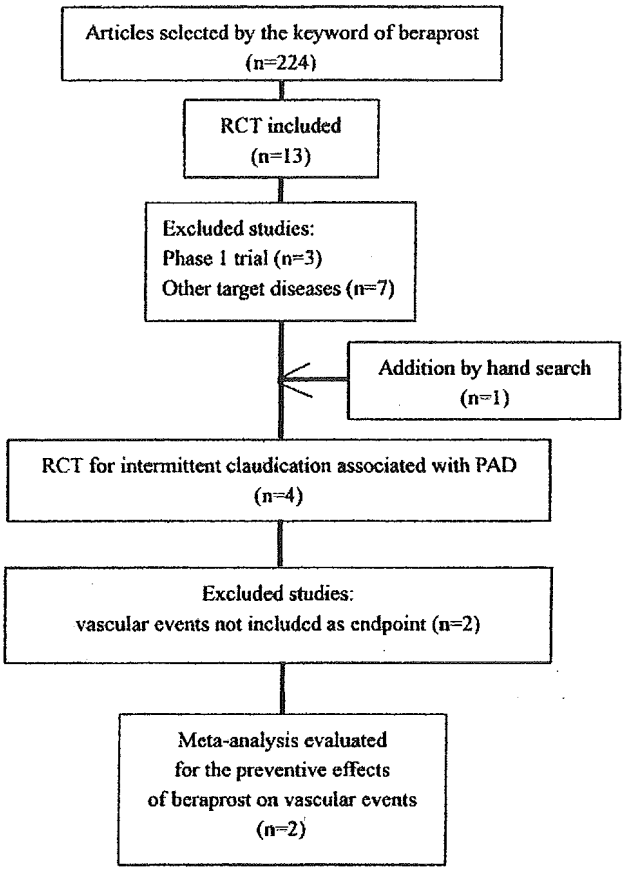


Fig. 1 Literature search process (1966-2003)

Methods

1. Trial selection

As shown in Figure 1, for the time period of 1966 to 2003, a total of 224 articles were retrieved by the Medline database using the keyword "beraprost". Limiting the search to the publication type of randomized controlled trial resulted in 13 articles. Among these 13 articles, 3 articles (Phase I trial) and 7 articles (other target diseases) were excluded as being unrelated to our study purpose. The remaining 3 articles[8,10,11] were thus regarded as candidates for evaluation. In addition, a single study[9] was selected by a hand-search method. Since two of the studies[8,9] did not deal with the endpoint of vascular events, the remaining two studies[10,11] were evaluated for the preventive effect of beraprost on vascular events. Of these two studies, one was the BERCI-2 trial[10] involving

549 patients in France and Italy, while the other involved 897 patients in the United States (US trial[11]). The primary outcome measure in these two trials was walking distance as evaluated by the treadmill test. In addition, vascular events were assessed as a secondary outcome measure.

2. General protocol

Both trials consisted of patients who met the inclusion criteria after a single-blind placebo run-in-phase and who were randomly assigned to receive either beraprost (40 μg t.i.d.) or a placebo (t.i.d.) for six months.

3. Outcome assessments

The present analysis used vascular events as outcome measures. Since the US trial[11] and the BERCI-2 trial[10] were conducted according to similar protocols, these two trials had the same definition of cardiovascular events including : death of cardiovascular origin (confirmed or sudden death), nonfatal myocardial infarction, unstable angina, stroke or transient ischemic attack, critical leg ischemia (rest pain necessitating an urgent medical intervention or a surgical procedure to avoid amputation), subacute critical ischemia (continuous rest pain for>2 weeks requiring analgesics), peripheral angioplasty, peripheral bypass surgery, and amputation at any level.

To avoid any potential bias by the investigator in event evaluation, in the US trial[11], all vascular events were adjudicated by an independent Critical Cardiovascular Events Committee, while, in the BERCI-2 trial[10], every potential vascular event was fully documented and evaluated blindly by three experienced cardiologists.

4. Study patients

Both trials had similar inclusion criteria with the exception of patient age (BERCI-2[10], 35-75 years ; US trial[11], 40-80 years) and concomitant medication (aspirin, clopidogrel, and ticlopidine were allowed in the US trial[11] but not in the BERCI-2 trial[10]).

5. Endpoints

The primary endpoint was defined as all vascular events for this meta-analysis. These events include lower limb deterioration and cardio/cerebrovascular events, which were assessed separately. Lower limb deterioration was regarded as a measure of PAD progression, while cardio/cerebrovascular events were evaluated to focus on ischemic heart disease and ischemic stroke.

6. Statistical analysis

Statistical analysis was performed according to the intention-to-treat population for the primary studies. P-values were computed using the Mantel-Haenszel chi-square test based on a 2×2 contingency table. A fixed effects model was used to estimate the pooled risk ratio based on a 2×2 table and its 95% confidence interval (CI) according to Mantel-Haenszel method. Heterogeneity between the trials was examined using the Cochran's Q-test[12]. A two-sided p-value of less than 0.05 was considered to be statistically significant. Statistical analyses were performed by using Comprehensive Meta-Analysis® software version 1.0.23.

Results

1. Baseline characteristics

At randomization after the run-in-period, the BERCI-2 trial consisted of 209 patients in the beraprost group and 213 patients in the placebo group, while the US trial had 385 and 377 in the beraprost and placebo groups, respectively. Baseline characteristics are shown in Table 1. As compared with the patients in the BERCI-2 trial, those in the US trial had slightly lower ankle-brachial indices (ABIs) and shorter maximum walking distances (MWDs). In addition, they were more likely to have hypertension, diabetes mellitus, or dyslipidemia. In the US trial, 65%, 6.3%, and 0.5% of the patients concomitantly used aspirin, clopidogrel, and ticlopidine, respectively.

2. Incidence of vascular events

Vascular events occurred in 29 patients (6.9%) in the BERCI-2 trial and 71 patients (9.3%) in the US trial. Cardio/cerebrovascular events other than lower limb events were documented in 7 patients (1.7%) in the BERCI-

Table 1 Baseline characteristics by treatment group for US trial and BERCI-2 trial

	US trial		BERCI-2	
	Beraprost	Placebo	Beraprost	Placebo
Number	385	377	209	213
Mean age (yrs)	65.9	65.7	63.3	61.5
Male	79%	74%	85%	84%
Mean duration of claudication (yrs)	6.4	6.6	6.4	5.3
Previous surgical treatment for PAD	23%	24%	28%	26%
Hypretension	73%	75%	41%	43%
Dyslipidemia	70%	71%	43%	46%
Diabetes	29%	29%	18%	18%
Smoking status				
Current smoker	33%	34%	34%	40%
Previous smoker	61%	58%	58%	51%
Non-smoker	6.2%	8.2%	8.6%	9.4%
Mean ABI	0.64	0.65	0.73	0.71
Mean MWD (m)	164	171	275	271
Mean PFWD (m)	85	90	130	134

ABI : ankle-brachial index, MWD : maximum walking distance,
PFWD : pain-free walking distance

2 trial and 45 patients (5.9%) in the US trial. Overall, the incidence was higher in the US trial.

Comparison between beraprost and the placebo revealed that beraprost was associated with a reduced incidence of vascular events in both trials ; events occurred in 10 beraprost-treated patients (4.8%) and 19 placebo-treated patients (8.9%) in the BERCI-2 trial while 28 beraprost-treated patients (7.3%) and 43 placebo-treated patients (11.4%) were reported to have had events in the US trial (Table 2). Both trials showed similar risk reductions for vascular events with 46.4% in the BERCI-2 trial and 36.2% in the US trial. The number needed to treat was also quite similar, 24 for the US trial and 25 for the BERCI-2 trial.

3. Meta-analysis

Figure 2 shows the results of the meta-analysis of the two trials examining vascular events. The pooled risk ratio was 0.608, indicating a significant risk reduction of beraprost on all vascular events (95%CI : 0.41 to 0.90, p=0.012). The pooled risk ratio for lower limb deterioration was 0.598 (95%CI : 0.34 to 1.06, p=0.079) and the pooled risk ratio for cardio/cerebrovascular events was 0.619 (95%CI : 0.36 to 1.09, p=0.085) ; these were statistically insignificant but similar to that for all vascular events. Heterogeneity among the two studies was not found in the risk ratio for any of these endpoints.

Discussion

1. Risk of vascular events in patients with PAD

The incidence of cardio/cerebrovascular events was 1.7% in the BERCI-2 trial[10] and 5.9% in the US trial[11], a finding that highlights an increased risk of cardio/cerebrovascular events in patients with PAD. The incidence of nonfatal cardiovascular events in patients with IC has been reported to be 2-4% annually[13]. The value for BERCI-2 was similar to the previously reported one ; however, the US trial gave a higher incidence only for six months.

In the Cardiovascular Health Study[14], ABIs was closely correlated to the number of patients with myocardial infarction, angina, and congestive heart disease. ABIs, smoking, diabetes, hypertension, white cell count,

Table 2 Summary of the vascular events in intention-to-treat population

	US trial		BERCI-2	
	Beraprost	Placebo	Beraprost	Placebo
Cardio/cerebrovascular event	**18**	**27**	**2**	**5**
Cardiovascular death	1	4		
Myocardial infarction	0	5		
Unstable angina	5	7		
Cardiovascular revascularization	7	7		
Cerebrovascular accident	5	4		
Limb deterioration	**10**	**16**	**8**	**14**
Worsening limb ischemia	6	8		
Limb revascularization	4	8		
Limb amputation	0	0		
Total	28/385 (7.3%)	43/377 (11.4%)	10/209 (4.8%)	19/213 (8.9%)
Risk reduction	36.2%		46.4%	
Number needed to treat	24		25	

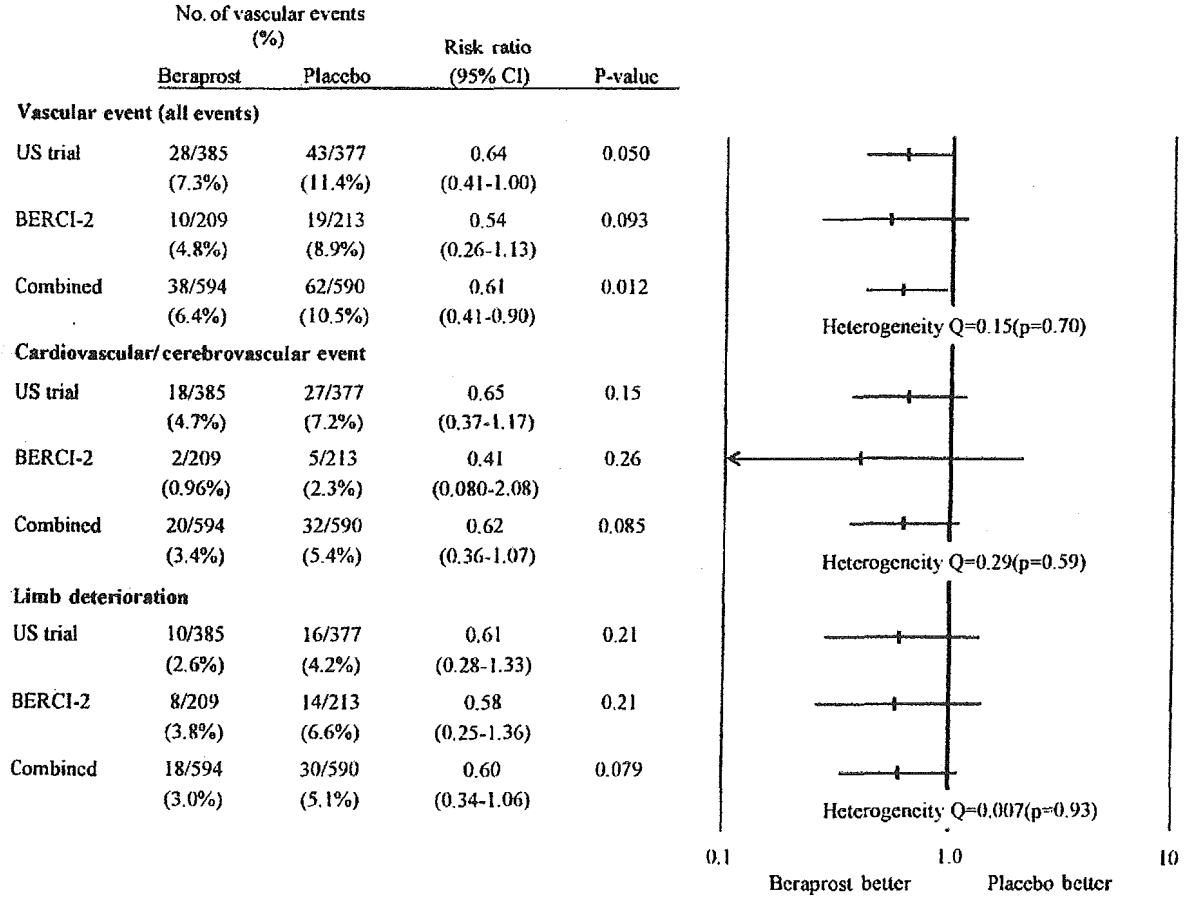


Fig. 2 Meta-analysis of two randomized trials of beraprost sodium therapy for vascular events

asymptomatic carotid disease and fibrinogen have all been reported as predictors of mortality[13].

The US trial included patients with lower ABIs and a high number of patients with diabetes mellitus, hypertension, or dyslipidemia. These factors may have affected the difference between the two trials.

2. Risk reduction of beraprost on cardio/cerebrovascular events and limb deterioraion

In both trials, the total number of vascular events was not statistically significant, but it was relatively low in the beraprost group. In the US trial, there was a significant reduction in the combination of cardiovascular death and myocardial infarction in the beraprost group. As expected, the meta-analysis of two trials has demonstrated the significant risk reduction of beraprost in vascular events. Analyses showed similar risk reductions of 39% ($p=0.012$) for overall events, 40% ($p=0.079$) for lower limb events, and 38% ($p=0.085$) for cardio/cerebrovascular events. Since stratification reduced the number of events and statistical power, these figures failed to reach significant levels. Taken together, the results suggest that beraprost may prevent the progression of arteriosclerosis not only in peripheral arterial disease but also in "systemic arterial disease".

A report by Antithrombotic Trialists' Collaboration[15] described 26 trials of antiplatelet agents in patients with IC due to PAD, estimating a 23% odds reduction for antiplatelet therapy. The present analysis with beraprost also gave a similar result. The goal of treatment in patients with intermittent claudication is to extend walking distance, and the prevention of the progression of lower limb disease is a therapeutic goal of PAD medications. The present meta-analysis showed promising effects of beraprost in preventing the progression of lower limb arteriosclerosis.

3. Relevance of these findings to PAD treatment in Japan

Ojiro and Yamazumi reported an epidemiological study of nursing homes for the elderly in Amami Island, Japan[16]. The three-year survival rate was 66.3% for patients with arteriosclerosis obliterans (ASO) and 74.3% for non-ASO individuals (p=NS). ASO was frequently associated with cardiovascular deaths, with the most common cause of death being acute myocardial infarction ($p<0.05$). As in other countries, ASO is a disease with a poor life prognosis in Japan.

For the life prognosis of patients with ASO, Miyazaki et al. reported a retrospective study of pharmacologic interventions[17]. In patients with ASO receiving various antiplatelet agents after undergoing femoral-peripheral artery bypass graft, a multiple logistic regression analysis including potential prognostic factors revealed that only beraprost significantly improved lifelong prognosis among antiplatelet agents such as aspirin and ticlopidine. This report suggests that beraprost also reduces vascular events in Japanese PAD patients.

These promising effects should be evaluated prospectively in future trials of beraprost with vascular events as the primary outcome. Six months is a widely accepted period for evaluating treadmill walking distance as a primary outcome. However, periods of a year or longer are suggested in such prevention trials to obtain clinical relevance.

4. Methodological limitation

The two selected studies[10,11] have utilized the log-rank test for comparison between groups. They also presented the p-value obtained by a log-rank test. However, they did not show a hazard ratio and have just shown the number of events per total number of patients. Thus, the information obtained from articles was nothing but several 2×2 contingency tables. The present meta-analysis should combine the hazard ratio across the studies since the time to event was a primary outcome. However, their detailed data was not presented in the articles. So that, there was only a way to combine the risk ratios computed by 2×2 contingency tables. The bias caused by using a risk ratio rather than a hazard ratio is considered to be

quite small since the two studies had a common 6-month follow-up and the hazard is considered to be constant during this period.

Acknowledgements

This study was partly supported by a grant-in-aid for scientific research from the Japanese Health and Labour Science (H15-Medicine-032).

References

1) Yang L, Yatomi Y, Satoh K, Ozaki Y. Inhibitory effects of beraprost on platelet aggregation. Comparative study utilizing two methods of aggregometry. *Thromb Res* 1999 ; **94** : 25-32.
2) Koh E, Morimoto S, Jiang B, et al. Effects of beraprost sodium, a stable analogue of prostacyclin, on hyperplasia, hypertrophy and glycosaminoglycan synthesis of rat aortic smooth muscle cells. *Artery* 1993 ; **20** : 242-52.
3) Tomiyama H, Arai T, Hirose K, et al. Effects of acute administration of beraprost sodium on parameters related to atherosclerotic vascular damage in coronary artery disease. *J Cardiol* 2004 ; **43** : 53-8.
4) Loosemore TM, Chalmers TC, Dormandy JA. A meta-analysis of randomized placebo control trials in Fontaine stages III and IV peripheral occlusive arterial disease. *Int Angiol* 1994 ; **13** : 133-42.
5) Hashiguchi M, Ohno K, Saito R. Studies on the effectiveness and safety of cilostazol, beraprost sodium, prostaglandin E_1 for the treatment of intermittent claudication. *J Pharmaceutical Society of Japan* 2004 ; **124** : 321-32.
6) Melian EB, Goa KL. Beraprost : a review of its pharmacology and therapeutic efficacy in the treatment of peripheral arterial disease and pulmonary arterial hypertension. *Drugs* 2002 ; **62** : 107-33.
7) Reiter M, Bucek RA, Stumpflen A, Dirisamer A, Minar E. Prostanoids in the treatment of intermittent claudication : a meta-analysis. *Vasa* 2002 ; **31** : 219-24.
8) Lievre M, Azoulay S, Lion L, Morand S, Girre JP, Boissel JP. A dose-effect study of beraprost sodium in intermittent claudication. *J Cardiovasc Pharmacol* 1996 ; **27** : 788-93.
9) Labs KH, Nehler MR, Roessner M, Jaeger KA, Hiatt WR. Reliability of treadmill testing in peripheral arterial disease : a comparison of a constant load with a graded load treadmill protocol. *Vasc Med* 1999 ; **4** : 239-46.
10) Lievre M, Morand S, Besse B, Fiessinger JN, Boissel JP. Oral Beraprost sodium, a prostaglandin I_2 analogue, for intermittent claudication : a double-blind, randomized, multicenter controlled trial. Beraprost et Claudication Intermittente (BERCI) Research Group. *Circulation* 2000 ; **102** : 426-31.
11) Mohler ER 3rd, Hiatt WR, Olin JW, Wade M, Jeffs R, Hirsch AT. Treatment of intermittent claudication with beraprost sodium, an orally active prostaglandin I_2 analogue. *J Am Coll Cardiol* 2003 ; **41** : 1679-86.
12) Sutton AJ, Abram KR, Jones DR, Sheldon TA, Song F. *Methods for Meta-Analysis in Medical Research*. Chichester : John Wiley, 2000 : 39.
13) Dormandy JA, Rutherford RB. Management of peripheral arterial disease (PAD). TASC Working Group. TransAtlantic Inter-Society Concensus (TASC). *J Vasc Surg* 2000 ; **31** (Suppl 1 Pt 2) : S1-S296.
14) Newman AB, Siscovick DS, Manolio TA. Ankle-arm index as a marker of atherosclerosis in the Cardiovascular Health Study. *Circulation* 1993 ; **88** : 837-45.
15) Antithrombotic Trialists'Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high-risk patients. *Br Med J* 2002 ; **324** : 71-86.
16) Ojiro M, Yamazumi K. The prevalence and natural history of atherosclerotic obliterance (ASO) in old-age home in Amami Island, three-year follow-up study. *Med J Kagoshima Univ* 2000 ; **52** : 1-6. (In Japanese)
17) Miyazaki K, Nishibe T, Sata F, et al. Prosthetic grafts for above-knee femoropopliteal bypass. A multicenter retrospective study of 564 grafts. *Int Angiol* 2002 ; **21** : 145-51.

Manuscript recieved November 29, 2004 ;
revised January 21, 2005 ;
accepted January 31, 2005

Jpn. J. Pharm. Health Care Sci.
一般論文 31(3) 203—210 (2005)

Progressive Bone Loss due to Androgen Deprivation Therapy for Prostate Cancer : A Meta-analysis

Shuji Shimada*[1,2], Naomi Yokoyama[3], Hideki Origasa[4], Hiroshi Tsuneki[1] and Ikuko Kimura[1]

Department of Clinical Pharmacology, Graduate School of Pharmaceutical Sciences, Toyama Medical and Pharmaceutical University[1]

Department of Pharmacy, The Hospital of Ishikawajima-Harima Heavy Industries Health Insurance Society[2]

Department of Pharmacoepidemiology, Graduate School of Medicine, Kyoto University[3]

Department of Biostatistics, Faculty of Medicine, Toyama Medical and Pharmaceutical University[4]

(Received November 22, 2004
Accepted January 4, 2005)

Hormonal therapy (androgen deprivation therapy) is the standard treatment for controlling prostate cancer, but adverse effects on bone health have been reported frequently. The aim of the present study was to evaluate the severity of progressive bone loss due to androgen deprivation therapy for prostate cancer through a meta-analysis. Relevant articles on this topic were selected using the Medline database and manual searches, and randomized controlled trials and open-labeled uncontrolled trials were performed. The overall mean loss in bone mineral density was estimated as the weighted mean of the percentage change from the initial bone density. The results of our systematic review showed that bone mineral density had decreased by 2.8% at the femoral neck, by 2.7% at the lumbar spine, and by 1.5% at the hip after 12 months of androgen deprivation therapy. The degree of the effect of androgen deprivation therapy versus the control was estimated to be 0.62 (95% confidence interval, 0.24 to 0.99; P=0.002) at the femoral neck; 0.58 (0.20 to 0.97; P=0.003) at the lumbar spine; and 0.89 (0.47 to 1.32; P<0.001) at the hip. These results provide evidence that androgen deprivation therapy for prostate cancer results in a rapid loss of bone mineral density, and increases the risk of osteoporosis and related fractures. In order to prevent this, it may be necessary to monitor the bone mineral density before and during therapy and administer agents that stimulate bone metabolism.

Key words —— prostatic neoplasms, androgen deprivation therapy, adverse effects, bone density, meta-analysis

Introduction

Prostate cancer is the most common cancer and the second leading cause of death from cancer among U.S. men[1]. Ever since Huggins and Hodges first recognized the hormonal dependence of prostate cancer 60 years ago[2], androgen deprivation therapy has remained central to the management of advanced disease. Also, early primary androgen deprivation therapy improves survival in men with locally advanced, nonmetastatic prostate cancer[3]. In several retrospective studies, androgen deprivation therapy has been reported to increase the risk of bone fractures in men with prostate cancer. The cumulative incidence rate of initial fracture 7 years after castration or diagnosis of prostate cancer was 28 % in patients treated by orchiectomy, and 1% in patients who did not undergo androgen deprivation therapy, respectively[4]. Osteoporosis and related fractures are complications of androgen deprivation therapy, because androgens exert actions on osteoblast proliferation[5], growth factor and cytokine production[6] and matrix protein production[7] via androgen receptors that are found on osteoblasts[8].

In women, the most common cause of osteoporosis is essential osteoporosis, which is age-related. By contrast, essential osteoporosis is rare in men, probably because they have a greater bone mass than women at all ages, a shorter life expectancy than women, and no distinct equivalent to menopause[9]. Glucocorticoids are widely used in the treatment of patients with chronic noninfectious inflammatory diseases, especially asthma, chronic lung diseases, rheumatoid arthritis and other connective tissue diseases, inflammatory bowel disease and in patients undergoing organ transplantation. Os-

1,4 富山市杉谷2630; 2630, Sugitani, Toyama-shi, 930-0194 Japan
2 中央区佃2-5-17; 2-5-17, Tsukuda, Chuo-ku, Tokyo, 104-0051 Japan
3 京都市左京区吉田近衛町; Yoshida-Konoe-cho, Sakyo-ku, Kyoto-shi, 606-8501 Japan

teoporosis and related fractures are among the most serious adverse effects of glucocorticoids; indeed, glucocorticoids are the most common cause of drug-related osteoporosis. Glucocorticoids decrease the intestinal absorption of both calcium and phosphate. The urinary calcium excretion is increased in glucocorticoid-treated patients, possibly due to a direct effect of the drug on the tubular reabsorption of calcium. Decreased gastrointestinal absorption and increased renal excretion of calcium can lead to secondary hyperparathyroidism, with elevated serum levels of parathyroid hormone[10]. Long-term exposure to glucocorticoids inhibits osteoblast proliferation, attachment of osteoblasts to bone extracellular matrix, and synthesis of both type I collagen and noncollagenous proteins by osteoblasts[11]. Chronic glucocorticoid therapy can result in significant loss of bone mass, especially at skeletal sites with a high proportion of trabecular bone, where bone turnover is the highest[12,13]. The American College of Rheumatology has summarized the available information regarding the pathophysiology, diagnosis, prevention and treatment of corticosteroid-induced osteoporosis, and provided recommendations for clinical practice[14]. On the other hand, information about the prevention and treatment of osteoporosis caused by androgen deprivation therapy is limited. The purpose of this article is to provide an objective and systematic review of the adverse effects of androgen deprivation therapy and the clinical relevance of androgen deprivation therapy in the treatment of prostate cancer.

Methods

1. Literature search

The National Library of Medicine (PubMed) was used to identify all clinical trials relating to the treatment of prostate cancer. We used the PubMed search strategy using the following search terms: prostatic neoplasms, gonadorelin, androgen antagonists, antineoplastic agents, orchiectomy, bone and bones, bone density, osteoporosis and fractures, as well as the term of clinical trials. Literature search was conducted from original articles published between the year 1966 and August 2003. The reference lists of studies included in the meta-analysis were manually collected to include any citations that were missed by the electronic searches.

2. Selection and data abstraction

Initially, all the randomized controlled clinical trials were selected for further assessment. We screened titles and abstracts from potentially eligible studies, and selected studies conducted on patients with prostate cancer as the subjects who were being initiated on treatment or were at the time under treatment with a gonadotropin-releasing hormone (GnRH) agonist, antiandrogen and orchiectomy. Two investigators independently assessed each article for eligibility, and any disagreement was settled by consensus. For each eligible study, we collected the information on study design, number of participants, mean age, type of prostate cancer, type of bone mineral density measurements, calcium supplement, type of androgen deprivation therapy, and the follow-up period. As regards to the study quality, a randomized controlled trial was rated the grade 'a', while a single arm trial of androgen deprivation therapy only or controlled trials with unknown randomization were rated the grade 'b' although all these trials were included into the analysis.

3. Outcome measures

The primary outcome measure was the mean loss in bone mineral density (in grams per surface unit, or sometimes, grams per volume of a circumscribed area [content]) that was obtained as a percentage change from the initial value. It was recorded at the femoral neck, lumbar spine and hip for each group (androgen deprivation therapy or control). Although any assessment of bone mineral density was made at the 6 months and/or 12 months after the initiation of therapy, the data at 12 months were utilized if both data were available.

4. Statistical analysis

All the analyses were performed according to the intention-to-treat principle. The pooled estimate of bone mineral density percentage change was estimated by the weighted mean of bone mineral density percentage changes where the weight was set as an inverse of square of the standard deviation (SD). When the mean percentage change of bone mineral density was not reported in the article, we approximated this value by dividing the reported absolute change of bone mineral density by its baseline value. Where standard error of the mean (SEM) was reported instead of SD, SD was calculated as SEM multiplied by $\sqrt{n}$ where n is the number of participants. Where no SD was reported, it was imputed by using the mean from the other trials. The effect size was defined by the mean difference of bone mineral density decrease between androgen deprivation therapy and control group during 6 or 12 months, divided by its SD. The value of effect size greater than 0 means a decreasing bone mineral density in the androgen deprivation therapy. The pooled effects size by androgen deprivation therapy in decreasing bone mineral density was estimated by using a fixed-effect model. Heterogeneity was investigated as in interaction between the study and its effect size in the above model.

Results

1. Literature search and critical appraisal

After a review of the abstracts in the search, 24 papers were found relating to androgen-deprivation-therapy-associated bone loss. Of these, we excluded 4 papers, because 2 were case reports and 2 were letters. Twenty of the 24 papers were potentially relevant, and were subjected to strict quality and eligibility assessment. Of the 20, 6 were excluded, because they lacked the bone mineral density values. A further 4 papers were excluded because the bone