る。ここで，転倒・転落事例の報告件数すなわち，転倒・転落により追加的医療費が発生したと考えられる件数：Ne，追加的医療費を確認できた件数：iNe，その確認できた追加的医療費：iCe および1件あたりの確認できた追加的医療費：iCe/iNe を示している。ここで，インシデントレポートシステムにより報告する際，報告者はインシデント内容を報告するとともに影響度レベルを入力する。レベル2以上を入力する場合，報告者は当該事例において何らかの検査や治療が実施されたことを認識したうえで入力しているはずである。したがって，追加的医療費：Ce は，この1件あたりの平均追加的医療費に転倒・転落件数を乗じたもので推計される。すなわち，Ce=Ne×iCe/iNe で求められる。

① 年度別影響度レベル別事象報告件数（表3）

インシデントレポート報告件数のうち，転倒・転落事例の件数は1,790件，レベル2以上の件数（追加的医療費の発生したと考えられる件数）：Ne は年度別にそれぞれ610件，565件，および615件であった。また，影響度レベル別にみると，いずれの年もレベル2がもっとも多く，順にレベル1，3a および3b であった。また，レベル5の事例が2007年度に1件認められたが，本研究では追加的な医療費が確認できなかったので検討事例から除外した。

② 影響度レベル別追加的医療費（表3）

追加的医療費の確認できた件数：iNe は，影響度レベル別年度別にみると，レベル2が2007年度77件（医療費確認割合（iNe/Ne×100）：28.0%（275件中)），2008年度46件（同様に17.4%（264件中））および2009年度82件（28.8%（285件中））であった。レベル3a について，同様に89件（78.8%（113件中)），41件（46.1%（89件中））および56件（58.3%（96件中)），レベル3b が11件（57.9%（19件中)），7件（87.5%（8件中））および16件（84.2%（19件中））であった。全体では1,790件中425件（23.7%）で全年度を通じて転倒・転落事例の約1/4で追加的医療費が確認された。

また，確認できた追加的医療費：iCe を影響度レベル別年度別にみると，レベル2について，2007年度736千円，2008年度449千円および2009年度841千円で，レベル3a について同様に1,076千円，500千円および727千円であった。また，レベル3b について，同様に2,755千円，1,002千円および3,952千円と影響度レベルの上昇とともに確認できた追加的医療費が増加していた。

さらに1件あたりの確認できた平均追加的医療費：iCe/iNe についても影響度レベル別年度別にみるとそれぞれ，レベル2が2007年度9.6±7.6千円（平均±標準偏差），2008年度10.7±9.7千円および2009年度10.3±7.2千円で，年度による有意差は認めなかった。レベル3a についても同様にそれぞれ年度別に13.1±19.5千円，12.2±13.1千円，および13.0±10.1千円で年度による有意差は認めなかった。レベル3b も同様に年度別に，250.1±353.8千円，143.1±184.5千円および247.0±269.5千円で，年度による有意差は認めず，手術治療など積極的な治療が必要なレベル3b は他のレベルと比較して医療費が高いことが分かる。確認できた平均の追加的医療費：iCe/iNe について全年度を通じてみると，レベル2は10.1±7.9千円，レベル3a は12.9±15.8千円，およびレベル3b は226.7±281.1千円であったことから，3年間の追加的医療費のレベル別の推計額：Ne×iCe/iNe について，レベル2は8,322千円，レベル3a は3,844千円およびレベル3b は10,428千円であった。したがって，3年間の追加的医療費の総額は，以上のレベル別の推計額の総計として求められ，その額は22,594千円と推計された。

ここで，影響度レベルに関係なく追加的医療費を算出すると，表3の合計の欄のように示される。2007年度の1件あたりの確認できた追加的医療費の平均：iCe/iNe は26.3±103.3千円でこれに追加的医療費が発生したと考えられる転倒･転落件数（Ne）を乗じて，2007年度1年間の追加的医療費の合計が推計され，その額は16,043千円である。一方，レベル別に確認できた追加的医療費の平均とその件数を乗じた，レベル別の1年間の追加的医療費の推計額は，それぞれ2,640千円，1,480千円および4,752千円で1年間の追加的医療費の推計額はこれらの総和で8,872千円であった。これと先に算出した16,043千円と比較すると約半分であった。2008年度，2009年度および全年度も同様の結果であった。

C. 影響度レベル別診療区分別医療費（表4）

わが国の医療費は，投薬，注射，処置・手術，検査，画像，入院費などから構成され，診療報酬表に詳細に定められている。表4は，確認された追加的医療費：iCe について，診療区分別影響度レベル別に示したものである。ここでは，今までの結果で年

表4　影響度レベル別診療区分別追加的医療費

影響度レベル（n）	2（205）	3a（186）	3b（34）	合計（425）
投薬	7,760（33） 235±182	41,772（77） 542±755	131,020（23） 5,697±8,599	180,522（133） 425±2,362
注射	33,720（9） 3,747±3,361	196,630（19） 10,349±18,615	161,610（17） 9,506±10,884	391,960（45） 922±5,221
処置・手術	21,530（7） 3,076±5,111	201,373（45） 4,475±8,564	6,192,190（15） 412,813±249,448	6,415,093（67） 15,044±88,686
検査	12,650（7） 1,807±766	16,490（15） 1,099±1,099	230,060（21） 10,955±10,224	259,200（43） 610±3,263
画像	1,950,640（195） 9,985±6,433	1,847,450（144） 12,830±7,763	972,640（34） 28,607±17,266	4,770,730（373） 11,217±10,184
その他	500（1） 500（1）	230（1） 230（1）	21,060（9） 2,340±2,038	21,790（11） 51±439
合計	2,027,000（205） 10,070±7,934	2,304,000（186） 12,859±15,772	7,709,000（34） 226,723±281,065	12,040,000（425） 28,579±98,426

度による相違が認められないことから，全年度を通じて検討した。

表4から，レベル2では画像に関する医療費は1,950,640円で合計（2,027,000円）の96.2%，件数についても205件中195件95.1%を占め，医療資源がもっとも投入されていた。また，投薬に関する追加的医療費は7,760円で合計のわずか0.38%であるが，件数は205件中33件16.1%で実施されていた。

レベル3aでは，レベル2と同様に画像にもっとも医療資源が投入されており，1,847,450円で合計（2,304,000円）の80.2%を占め，続いて処置・手術の201,373円，8.74%，注射の196,630円，8.53%と続いている。また，件数でみるとレベル3a事例で，画像を実施した件数は186件中144件（77.4%）でもっとも多く，投薬については，追加的医療費に占める割合はわずか1.81%（41,772/2,304,000円）であるが，186件中77件（41.4%）に実施されていた。

また，レベル3bでは，骨折に対する観血的手術など積極的治療が施行されることから，処置・手術に関する医療費は6,192,190円で，追加的医療費合計（7,709,000円）の80.3%を占めていた。画像検査を実施したのは全例で34件，その追加的医療費は972,640円で合計（7,709,000円）の12.6%であった。また，処置・手術の追加的医療費は6,192,190円で金額が多いものの，34件中15件，50%に実施されていた。

また，影響度レベル別の1件あたりの平均診療費は，レベル2が10,070±7,934円，レベル3aが12,859±15,772円，およびレベル3bが226,723±281,065円で，レベル3aの医療費はレベル2より有意に高く（p=0.027），レベル3bはレベル3aより有意に高いことが分かった（p<0.001）。影響度レベルに関係なく全体でみると，1件あたりの平均診療区分別追加的医療費について，もっとも高いのは処置・手術に関するもので；15,044±88,686円（67件），ついで画像の11,217±10,184円（373件）であった。

レベル3bの画像には，レベル3bの追加的医療費は合計7,709,000円の12.6%，972,640円が必要であった。また，件数的には画像が34件すべての症例に実施され，続いて投薬は34件中23件（67.6%）に，検査は21件（61.8%）に，注射は17件（50.0%）に，医療費の大きい処置・手術は15件（44.1%）にすぎなかった。全体でみると，画像については，425件中373件（87.6%）が実施されており，転倒・転落事例には画像診断が不可欠であることが示唆された。

D. 追加的医療費確認件数と確認された追加的医療費合計に対する影響度レベル別追加的医療費の割合（図3）

確認できた追加的医療費の発生した件数：iNeおよび確認できた追加的医療費：iCeの割合を影響度レベル別年度別に示したのが図3である。転倒・転落による追加的医療費が確認できた件数について，レベル2については，2007年77件（177件中43.5%），2008年46件（94件中48.9%）および2009

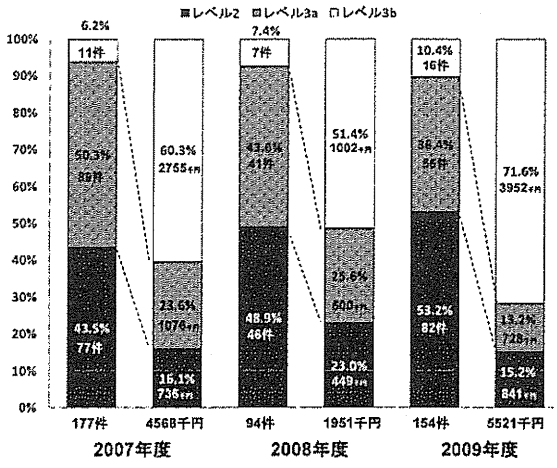

図3 追加的医療費（右）とその件数（左）の割合

年82件（154件中53.2%）であり，同様に，レベル3aは2007年89件(50.3%)，2008年41件(43.6%)および2009年56件（36.4%）であった。また，レベル3bについては，2007年11件（6.2%），2008年7件（7.4%）および2009年16件（10.4%）であった。一方，確認できた追加的医療費について年度別にみると，影響度レベル別に追加的医療費全体に占める割合および金額をみると，レベル2は2007年16.1%（736/4,568千円），2008年23.0%（449/1,951千円）および2009年15.2%（841/5,521千円）で，同様にレベル3aは2007年23.6%(1,076/4,568千円)，2008年25.6%（500/1,951千円）および2009年13.2%（728/5,521千円）であった。また，レベル3bについて，2007年は60.3%（2,755/4,568千円），2008年は51.4%（1,002/1,951千円）および2009年は71.6%（3,952/5,521千円）を占めた。すなはち，報告件数の少ないレベル3bの追加的医療費がもっとも高いことが分かった。

以上の結果をまとめると，

① 3年間で報告された転倒・転落件数は1,790件で，そのうち425件（ΣiNe）で原疾患の医療費とは別の追加的医療費が確認され，その総額（ΣiCe）は約12,000千円であった。

② 確認できた1件あたりの追加的医療費は，影響度レベル2で10.1千円，レベル3aで12.9千円，およびレベル3bで226.7千円であった。この結果から，それぞれの影響度レベルの追加的医療費の合計の推計額（ΣNe×ΣiCe/ΣiNe）は，影響度レベル別に，レベル2は10.1×824=8,322千円，レベル3aは12.9×298=3,844千円およびレベル3bは226.7×46=10,428千円で，3年間の追加的医療費合計の推計額はその総和で22,594千円であった。したがって，1年間の転倒・転落によって生じるあらたな医療費は7,530千円であると推計された。ただし，影響度を考慮しない場合，1年間の追加的医療費は51,194/3=17,100千円で，その2倍以上の費用となることが推測された。

③ 確認できた追加的医療費全体に占める影響度レベル別の割合は，それぞれレベル2が16.8%（2,027/12,040千円），レベル3aが19.1%（2,304/12,040千円），およびレベル3bが64.0%（7,709/12,040千円）であった。

④ 確認できた追加的医療費を診療区分別にみると，影響度レベル2および3aで画像がそれぞれ96.2%および80.2%を占め，影響度レベル3bでは処置・手術が80.3%を占めた。

⑤ 処置・手術費用の違いは手術件数が2007年度5件，2008年度2件，2009年度7件であり，その件数の違いであると考えられた。

IV. 考　　察

わが国の医療安全活動は，1999年の大学病院における医療事故を契機にはじまったと考えてよい[13]。それから10年以上が経過したが，医療安全活動によって医療が安全になったというエビデンスはわれわれ医療者側から提供されていない。前述したように，わが国においては，2002年10月の院内報告制度の整備の義務化によって，今では各病院において，インシデントレポートシステムが充実し，それらの蓄積されたデータから医療安全に資するエビデンスを提供するのもわれわれ医療者の使命でもある。

一方，超高齢者社会となっているわが国では高齢者人口が増加の一途をたどり，医療費の増大に歯止めが掛っていない状況である。このような医療・社会環境下において，医療費適正化政策のもと，限りある医療資源の有効利用の観点から，医療機関においても効率的な運営が不可欠となっている。また，院内で発生したインシデント・アクシデントによって患者が傷害を受けた場合，患者・家族の権利意識の高揚から，それによりあらたに生じた，本来の原

疾患の医療費とは異なる医療費については，本院においても患者・家族がその支払いに応じないケースが散見されている。とくに，患者の転倒・転落は院内における有害事象や傷害の主たる原因となっている[14]。しかも，転倒・転落が発生すると，在院日数が延長し，医療費が高くなることは免れない[15,16]。

そこで，本研究では，転倒・転落によりあらたに生じた医療費に関する基本的データとして，転倒・転落事例をインシデントレポートシステムから抽出し，それらの事例について医事データを利用して「転倒・転落に起因する追加的医療費」を求めることとした。しかも，本研究は，調査の大部分はインシデントレポートシステムや医事データを利用することで遂行可能であり，他の医療機関でも利用可能な研究といえる。

ところで，本院で2007年～2009年度までに報告されたインシデントレポート件数は，年度別に2,760件，2,559件および2,398件であった。そのうち転倒・転落事例は，610件（22.1%），565件（22.1%）および615件（25.6%）を占めていた。本研究における転倒・転落件数は従来の報告と大差がなく[6]，また，米国の9病院での調査によれば，2001年～2003年の3年間における転倒・転落の報告8,974件のうち，それぞれ2001年2,810件（31.3%），2002年2,961件（33.0%），2003年3,203件（35.7%）であることから，本院の発生件数は妥当であると考えられた[17]。また，2007～2009年度での転倒・転落の発生率をみると，3年間を通じて1.87患者・日であった。Morseらによれば，急性期病院での転倒・転落の発生率は2.2-7.0/1,000患者・日であり，スイスの大学病院（800床）での調査では，26,643入院，236,307患者・日で転倒・転落事例は634例，全転倒の発生率は2.68/1,000患者・日であったと報告されている[18,19]。

一方，わが国のある大学病院（1,240床）で年齢60歳以上の対象患者1,280人における1ヶ月間のprospective studyによると転倒・転落事例の発生率は，転倒は1.2件/1,000患者・日，転落は0.3件/患者・日と比較すると3年間の平均発生率1.87件/1,000患者・日は多い印象も受けるが，前述と同様，比較のためには，都道府県別高齢化率の推移（平成16年高齢化率　京都府：19.7%，福岡県：19.2%）や全入院患者に対する高齢患者の割合も考慮する必要がある[20,21]。

また，本院（1,254床）での転倒・転落事例はインシデントレポートによると，1年間に平均597件であった。前述の報告によれば，1,240床の大学病院で1ヶ月の間に転倒，転落を合わせて45件の事例が発生している[20]。これを単純に1年間に換算すると540件であり，両者を比較してもほぼ同数であることから，病院の規模や性格，入院患者の高齢化率も考慮すると両院の発生率はほぼ妥当であると考えられる。

ところで，入院患者の転倒・転落により，あらたに生じる医療費は，冒頭でも述べたように，米国では保険会社が予防可能な事例ついては保険料支払いに応じない時代になっているほか，わが国でも患者や家族は転倒・転落の原因が病院側にあるとして，その医療費の支払いを拒否する時代に入っており，本院でも同様の経験をしている[5]。これらの，転倒・転落に起因する，原疾患の医療費とは別のあらたな追加的医療費は，保険者や行政の立場ばかりでなく，医療提供者側とくに病院管理者の立場からすると，適切で健全な病院経営のためにはそれを把握しておく必要がある。しかしながら，原価計算による手法では，診療・看護による医師や看護師，その他のコメディカルスタッフの人件費などを求めることも含め，この追加的医療費を算出できる状況にはない。

本研究では，対象の3年間での転倒・転落報告数1,790件のうち，追加的医療費が確認できた件数：iNeは425件（23.7%）で，確認できた追加的医療費総額：ΣiCeは12,040千円/3年間から求められる，1件あたりの確認できた平均追加的医療費：ΣiCe/ΣiNeは28.6±98.5千円であった。確認できた平均追加的医療費についてレベル別にみると，レベル2は10.1±7.9千円，レベル3aが12.9±15.8千円およびレベル3bが226.7±281.1千円であった。O'Connorらの報告によれば，2001年から2004年までの，15件の解決費用（settlement cost）の総額は4.6万ドル（約4,600千円）であったことから1件あたりの費用は307千円であった計算となる[22]。本研究では，レベル3b事例がこれに相当するものと考えられ，1件あたりの追加的医療費は226.7±281.1千円で，医療制度や医療環境の相違から安易な比較は禁物であるが，O'connorの報告とは大差がないと考えられた。また，Batesらによる後向きケース・コントロール研究によれば，ケース群とコントロール群の医療費の差が$4,233（約423千円）

であったことから，これが，本研究の1件あたりの追加的医療費（約286千円）に相当すると考えられ，これも上記と同様，大差はないものと考えられた[15]。

一方，国内の研究のうち，上岡らの報告によると，転倒における症例とその医療費および自己負担額について，入院を要した症例6例のうち，手術症例3例，手術のない症例3例と通院のみ1例が検討されている[11]。手術症例3例について，入院医療費は1症例あたり217,443円であり，これら事例は本研究における影響度レベル3bに相当し，その追加的医療費の1事象あたりの平均は226.7±281.1千円で大差がない[11]。また，小林らの研究では，転倒・転落のインシデントの医療費は，28事例についてその平均は9,435±6,910円（中央値8,324円，最小値2,040円，最大値42,970円）で，これらの事例は本研究の影響度レベル2に相当する[10]。本研究の影響度レベル2の追加的医療費の平均値は10,170±7,934円で小林らの結果と大差ない[10]。ただし，小林らの研究では転倒・転落のアクシデント事例（本研究の影響度レベル3bに相当）は含まれていない。さらに，Shibuyaらの研究では転倒・転落事例4例を含む影響度レベル3a事例15例について，その平均の有害事象コストは186,357円であった[12]。また，影響度レベル3aが4例，3bが12例，4が2例および5が1例を含む全19例の転倒・転落事例について，その有害事象コストの平均値は291,753円で，影響度レベル別での比較は困難であるが，本研究では28.6千円で，かけ離れた結果ではないと考えられる[12]。

ただし，例えば年間の追加的医療費の総計を検討する際，影響度レベルを無視して算出した場合と影響度レベル別に算出したものを総和したものとは2倍以上の開きがあるので，影響度レベル別に算出することが推奨される。

つぎに，表4から，診療区分別追加的医療費を影響度レベル別にみると，レベル2では追加的医療費の発生した205件中195件で画像検査の実施が確認され，金額も確認できた追加的医療費合計の96.2%（1,950,640円/2,027,000円）を占めていた。その他の診療行為は画像のつぎに投薬が実施されているが医療行為の発生した205件中33件（16.1%）でその医療費も合計のわずか0.38%（7,760円/2,027,000円であった。

レベル3aでの診療行為をみると，実施を確認できた件数の多い順に画像144件（80.2%，144/186），投薬77件（41.4%），処置・手術が45件，注射が19件の順であった。しかし，その追加的医療費でみると，多い順に画像は1,847,450円，医療費合計の80.2%（1,847,450円/2,304,000円）を占めていた。ついで，処置・手術に8.7%（201,373円），注射8.5%（196,630円）であった。ここで，それぞれの診療行為の実施を確認できた件数で除した平均の追加的医療費でみると，画像は12,830円，注射が10,349円と続き，処置・手術は4,475円であり，レベル3aは，画像についで注射の追加的医療費が高いことが分かる。

つぎにレベル3bでの診療行為について，追加的医療費を確認できた34件のうち各診療行為を実際に行った件数は，画像34件（100%，34件中34件），投薬23件（67.6%），検査21件（61.8%），注射17件（50%），処置・手術15件（44.1%）であった。しかし，各診療行為の実施を確認できた件数の平均の追加的医療費は，処置・手術は412,813円がもっとも高く，ついで画像28,607円，検査10,955円，注射9,506円であり，処置・手術に医療資源がもっとも投入されていることが分かる。

また，影響度レベルと追加的医療費の関係を検討すると，図3の結果から，いずれの年度においても影響度レベルと追加的医療費の関係について，レベルが高いほどその件数は少ないものの，追加的医療費は増加することが分かった。

つぎに，影響度レベルが高くなると追加的医療費が増加することから，レベル3b事例34件について検討した。表5は，34件の内訳を示している。その属性をみると，男女比はそれぞれ17件ずつで1:1，平均年齢は男69.8±13.0歳，女78.2±10.3歳で統計学的有意差を認めた（p=0.045）。それぞれの追加的医療費は，男196,295±232,899円，女257,151±326,686円で有意差を認めなかった（p=0.536）。また，疾患名をみると女はすべて骨折に関係し，大腿骨骨折は女が8件，男が5件を占めていた。大腿骨骨折は，手術をともなうことが多く，その追加的医療費が高いことが分かった。一方，男は頭部外傷に起因するものが6件をかぞえ，手術をともなうため，他の疾患より追加的医療費が高い。この傾向は，上岡らの報告とも一致する[9]。

ところで，本研究では転倒・転落に起因する追加的医療費は，インシデントレポート報告書の【発生時の対応】をもとに，診療録から転倒・転落の発生

表5　3b事例の内訳

男（17例）：69.8±13.0歳	
ICD-10疾患名（度数）	追加的医療費（円）
脳内出血（2）	116,415±91,549
頭部打撲裂傷（1）	129,600
脳挫傷（1）	106,960
急性硬膜下血腫（1）	786,960
外傷性くも膜下出血（1）	5,780
肩脱臼（1）	38,270
左眼窩骨折（1）	25,960
顔面骨折（1）	26,410
上腕骨骨折（1）	38,480
第5指基節骨骨折（1）	11,710
大腿骨頚部骨折（1）	390,310
大腿骨転子部骨折（3）	203,830±245,645
大腿骨骨折（1）	426,300
膝蓋骨骨折（1）	505 960
平均±標準偏差	196,295±232,899

女（17例）：78.2±10.3歳*	
ICD-10疾患名（度数）	追加的医療費（円）
上肢骨折（2）	2,1770±7,439
尾骨骨折（1）	143,900
橈尺骨骨折（1）	28,420
左橈骨遠位端骨折（1）	6,490
大腿骨頚部骨折（8）	243,763±246,806
大腿骨転子部骨折（3）	756,186±323 147
足背骨折（1）	60,060
平均±標準偏差	257,151±326,686#

*男女の年齢は，有意差を認めた（p=0.045）
#追加的医療費の平均は，有意差を認めない（p=0.536）

を確認し，医事データによりその際行われた診療行為に基づく医療費を算出し，推計したものである。その際，もっとも留意すべきは，追加的医療に使用された薬剤や医療行為が確認できないことである。報告者は，何らかの検査や医療行為が行われていることを認識しているからこそ，その事例が影響度レベル2以上の判断を行っているのであるから，医療費が確認できなくとも追加的医療費を算出する際には，レベル別の件数を考慮に入れる必要がある。では，なぜ医療費が確認できないのか，そのもっとも大きな理由は検査や医療行為に必要な主たる薬剤はオーダーが必要であり，そのオーダーのあるものは医事データや診療録に記録が残っているから，事後でも確認が可能である。ところが，病棟配置薬を使用したり，あるいは救急カートにある薬剤を使用した場合には，その記録が残らない。この問題は，転倒・転落以外の有害事象の調査でも同じことが指摘されている。この点については病院経営上もさることながら，研究上の限界として今後解決すべき問題と考えている。

以上より，本院における転倒・転落事例の発生は他の医療施設と大差なく，1年あたりの追加的医療費の推計額は約700万円（22,594千円/3年間）で，レベル別の1件あたりの追加的医療費は，それぞれレベル2は約1万円，レベル3aは約1万3千円およびレベル3bは約23万円であった。また，画像は約90%の事例で実施され，レベル3bは，とくに手術治療を実施する必要があるため，追加的医療費全体の約80%を占めていた。とくに，3b事例では大腿骨骨折が多く，約半数の16件であった。

V. 結　　語

インシデントレポートで報告される事例のうち，転倒・転落に起因する，あらたな追加的医療費を本院で管理されている医事データを用いて算出することができた。追加的医療費は年間約700万円が必要であると推計され，また，レベル3b事例にその約80%が投じられていることから，かりに転倒・転落が発生してもレベル3b，とくに大腿骨骨折や頭部外傷とならない医療安全対策を講じる必要があると考えられた。

この結果は，健全な病院経営や適切で的確な医療安全活動に資する非常に意義ある研究で，しかも，他の医療機関でも利用可能な研究である。

以上の要旨の一部は，ISPOR 15th Annual International Meeting（2010年5月，米国ジョージア州アトランタ），第12回日本医療マネジメント学会学術総会（2010年6月，札幌）ならびに第48回日本医療・病院管理学会学術総会（2010年10月，広島）にて発表した。

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EXTRA MEDICAL COSTS DUE TO FALLS BY USING INCIDENT REPORTING AND ADMINISTRATIVE PROFILING DATA AT A TEACHING HOSPITAL IN JAPAN : A RETROSPECTIVE CASE STUDY

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Medical costs following incidents and accidents within hospitals are not linked with primary diseases, and these costs may be borne by hospitals where patients are injured. It is therefore very important for policy makers and hospital managers to recognize the actual situation of additional medical costs for incidents. Cases with over level two injuries and their associated medical costs were explored over three years.

We collected 7,717 incident reports between 2007 and 2009 at Saint Mary's Hospital in Kurume-City, Fukuoka, Japan. Their reports included 1,790 cases for Falls/Slips. There were 824 cases for Falls/Slips classified as level 2,298 cases for level 3a, and 46 cases with level 3b.

At the injury level, average additional medical costs were 10,070±7,934 JY* (level 2, 205 cases), 12,859±15,772 JY (level 3a, 186 cases), and 226,723±281,065JY (level 3b, 34 cases), and there were statistically significant differences among them (2 and 3a : p=0.027, 3a and 3b : p<0.001). Average medical costs were directly calculated from the insurance medical fee schedule under the social insurance system.

As a result, the total amount of additional medical costs for Falls/Slips is estimated to be seven million JY at our hospital, as additional medical costs are 2.8 million JY with level 2, 1.3 million JY with level 3a, and 3.5 million JY with level 3b. Therefore, it is suggested that patient safety activities need to be conducted in order to prevent patients with level 3b injuries from Falls/Slips.

*JY=Japanese Yen

Key words : additional medical costs/slips and falls/injury level/incident reporting system/administrative profiling data/teaching hospitals

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EDITOR'S CHOICE

Design and development of an international clinical data exchange system: the international layer function of the Dolphin Project

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ABSTRACT

Objective At present, most clinical data are exchanged between organizations within a regional system. However, people traveling abroad may need to visit a hospital, which would make international exchange of clinical data very useful.

Background Since 2007, a collaborative effort to achieve clinical data sharing has been carried out at Zhejiang University in China and Kyoto University and Miyazaki University in Japan; each is running a regional clinical information center.

Methods An international layer system named Global Dolphin was constructed with several key services, sharing patients' health information between countries using a medical markup language (MML). The system was piloted with 39 test patients.

Results The three regions above have records for 966 000 unique patients, which are available through Global Dolphin. Data exchanged successfully from Japan to China for the 39 study patients include 1001 MML files and 152 images. The MML files contained 197 free text-type paragraphs that needed human translation.

Discussion The pilot test in Global Dolphin demonstrates that patient information can be shared across countries through international health data exchange. To achieve cross-border sharing of clinical data, some key issues had to be addressed: establishment of a super directory service across countries; data transformation; and unique one—language translation. Privacy protection was also taken into account. The system is now ready for live use.

Conclusion The project demonstrates a means of achieving worldwide accessibility of medical data, by which the integrity and continuity of patients' health information can be maintained.

INTRODUCTION

Clinical data exchange provides the ability to move clinical information electronically across organizations, while maintaining the meaning of the information being exchanged.[1 2] Through the mutual provision of clinical data from disparate medical information systems, not only can a health enterprise offer more timely medical treatment, reduce costs, and make maximum use of medical resources, but it can also maintain the consistency and accessibility of patients' health information, thereby ensuring continuity of treatment, reducing medical errors, and improving the quality, safety, and efficiency of healthcare services.[3–7]

However, several barriers, such as communication, standardization, and interoperability, remain to implementing clinical data exchange across organizations. Technically, the lack of healthcare information technology standards and inter-system communication are the major problems that all countries face.[8] Although there are industry standards, such as HL7 CDA and CEN 13606, it is still necessary to localize the standards to suit the needs of a specific country or area.[9–13] Both the adoption and further development of international standards are essential for clinical data exchange. Beyond that, there are additional non-technical issues, such as financial support, competition, current property preservation, and work flow regulation.[7 8 14 15] For the above reasons, most clinical data exchange at present occurs between organizations within a regional system, with some occurrences at a national level.[16–32]

Because people travel around the world far more than ever before, the demand for clinical data exchange across national borders is becoming much greater. According to statistics, 348 million people crossed the borders of China in 2009, including 43.73 million foreigners.[33] Considering the great population of foreign travelers, the need to visit a hospital abroad is quite common and makes international clinical data exchange not only necessary, but also useful in helping doctors access patients' health information in order to provide precise assessments and appropriate treatment plans. The healthcare information generated abroad can either be preserved at a local clinical data center or sent to another electronic health record (EHR) system where the patient is referred. In this way, the integrity and continuity of patients' health information can be maintained.[34–37]

This report presents the collaborative work of Zhejiang University in China and Kyoto University and Miyazaki University in Japan concerning the design and development of an international clinical data exchange system using medical markup language (MML). This system is known as Global Dolphin, an international layer function of the Dolphin Project.[38] We also report on a pilot study of this application.

BACKGROUND

Medical markup language

In 1995, the Japan Association for Medical Informatics, the 'Electronic Health Record Research Group', published an electronically exchangeable medical data standard named MML, which uses the idea of exchanging data with attributes.[39–43]

Since 1998, MML has been successfully adopted by the Dolphin Project as a clinical data exchange standard.[38] In addition, a localized Chinese version

of MML has been created, which makes the exchange of medical data between Chinese health institutions possible.[44 45]

Because of the similarity of healthcare work flows and medical records between China and Japan, we adopted MML as the clinical data exchange standard in this project.

Dolphin Project

The Dolphin Project was proposed in 1998 as a cooperative regional clinical system. The intent was to establish data centers for storing medical information in regional units, creating EHR accounts for each patient, and sharing medical information based on MML, HL7, or other languages. In 2001, the Dolphin Project was adopted by, and developed cooperatively in, the prefectures of Miyazaki and Kumamoto.[46 47] Later, both Tokyo and Kyoto deployed the system, with the aim of providing practical EHR services.[48 49]

The Dolphin Project has three stages of development[50]: (1) the regional-level system named iDolphin which corresponds to a regional EHR; (2) the national-level system named Super Dolphin which corresponds to a National Health Information Network[51]; and (3) the international-level system named Global Dolphin as an international clinical data exchange.

The founding of the inter-organizational project

Zhejiang University, Kyoto University, and Miyazaki University have a long-term collaborative relationship in many research areas, and the field of medical informatics is an important one of these joint efforts. The cities of Hangzhou, Kyoto, and Miyazaki where the universities are located are famous historic and tourist cities. In 2009, 293 700 Japanese tourists visited Hangzhou, with an average stay of 3.08 days; Japanese tourist occupancy in Hangzhou is 9% of all Japanese tourists in China.

In October 2006, the three universities signed a contract regarding the cooperative research of international clinical data exchange; by the end of 2007, as a basis for international clinical information exchange, the iDolphin-based Xizi Regional Clinical Information Center (XRCIC), which was equivalent to those in Kyoto and Miyazaki, was deployed and in operation at Zhejiang University, Hangzhou, China. The early phase of the Dolphin Project was supported by Japanese government funding in 2001, and the international layer function of the Dolphin Project was mainly supported by Chinese government funding.

General objectives

Unlike domestic health information exchange, international clinical data exchange has to adapt to different healthcare work flows, convert the format of medical records, establish a super directory service across countries, and translate documents from the source language to the destination language. Beyond these major issues, there are additional concerns, such as data security, privacy protection, image interoperability, and the physician interface, to be resolved. Figure 1 shows a general map of the whole Dolphin Project, including Global Dolphin, which cooperates with iDolphin and Super Dolphin. Using these systems, patients and physicians can exchange and share clinical information between different countries.

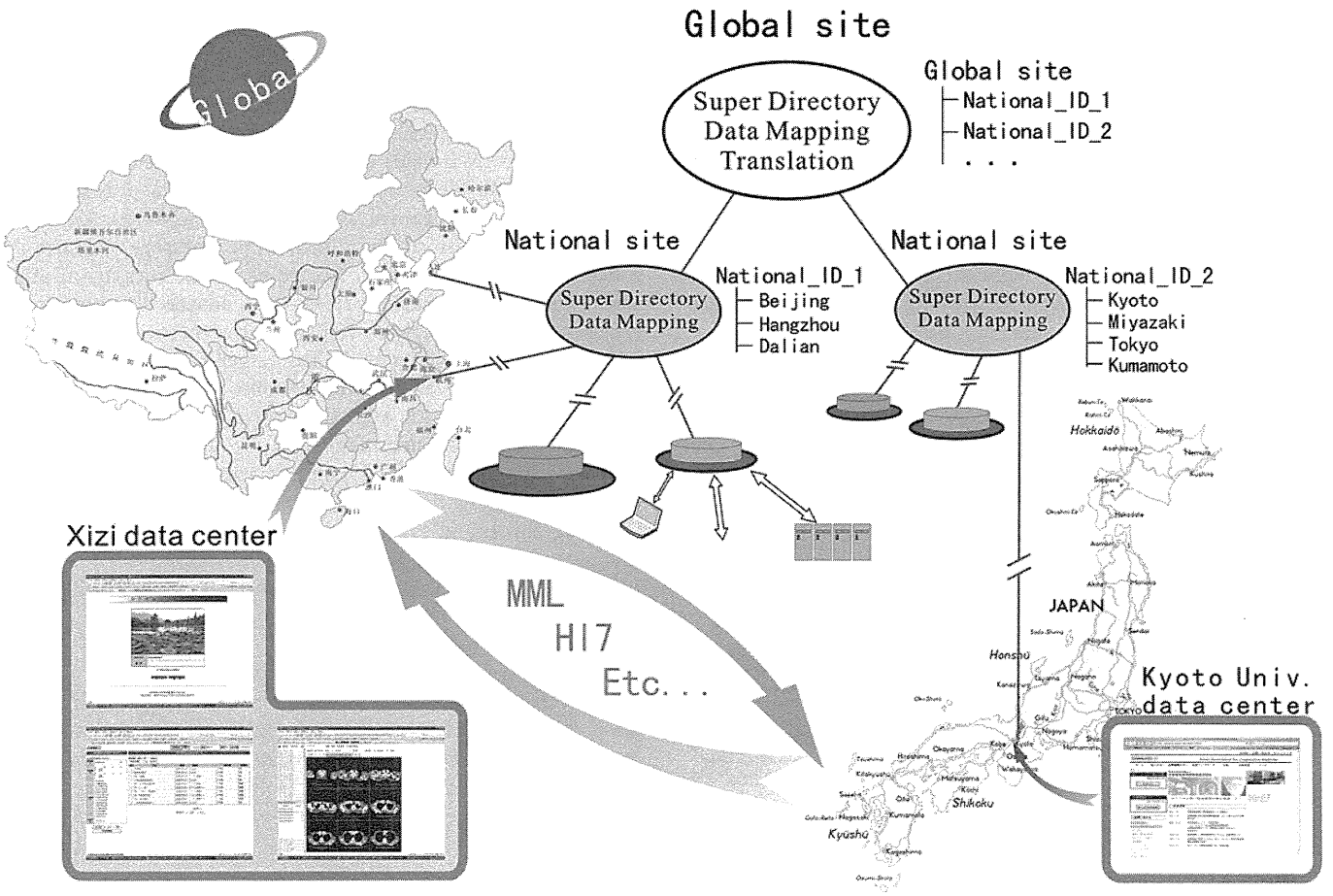

Figure 1 A general map of the entire Dolphin Project, including Global Dolphin. MML, Medical markup language.

METHODS

System design overview

The clinical data exchange workflow is shown in figure 2. Before a person travels abroad, he/she submits an application for his/her information to be linked to Global Dolphin and is given a unique global ID so his/her medical records can be queried from the international directory service at locations around the world. In addition, the translation of the record text could be performed beforehand. When the person goes to a hospital in another country, physicians with authorization can query his/her information from Global Dolphin using the global ID through a local site—for example, the XRCIC. The person's medical records will then be acquired from all of the national-level systems linked to Global Dolphin. If the person has not submitted an application for a global ID, Global Dolphin can still use his/her national ID or regional ID to query directly from the national-level system where the person lives and find the information required. In such a case, however, the free text-type paragraphs in the medical records cannot be immediately displayed in the destination language because the translation work is not performed in real time. The detailed clarification is in section 'E. Translation'.

Localized Xizi regional clinical information center

In October 2007, we installed and implemented an iDolphin system at Zhejiang University in China to test clinical data exchange between China and Japan; by the fall of 2008, all of the portal sites and applications had been translated into a Chinese version. In September of 2010, this Chinese version of iDolphin was connected to a localized electronic medical record (EMR) system and then transformed into a localized regional clinical information center; the web portal is entitled Xizi Net (see online supplementary figure 1).

International directory service

Among the three levels of the Dolphin Project, the patients' medical records actually existed at the regional-level clinical information center. In this way, when a patient visits doctors at multiple institutions in different regions, his/her information will be collected and preserved at different data centers. A directory service is needed to ensure the consistency and continuity of the patient's medical records and make his/her clinical data an entire collection to offer to a patient-centered service. A lightweight directory access protocol is used to build a single sign-on system; this links together the same person's respective accounts with his/her medical records under each account in different regional data centers. In this way, a user who logs into any of the data centers can access all of the clinical information in an integrated form.

In Global Dolphin, an international directory service is set up using the OpenLDAP [52] software at the XRCIC. In the directory service, each entity, such as a patient or an institution, is considered an object; information about a particular resource, such as a medical record, image, or facility, is stored as an attribute of that object. Information within objects is secured by the access control list, so that only users with the appropriate permission are able to access it. In Global Dolphin, when the patient travels to another country, his/her original information organized in different objects administered by each regional center will be mapped by the international directory service, enabling queries from the local data center where he/she is presently located.

The international directory service is a very important infrastructure for achieving integration of health records around the world, and making clinical data exchange possible among different countries.

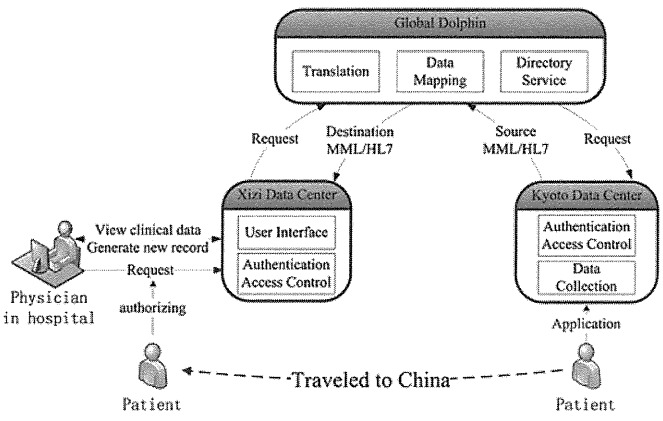

Figure 2 The workflow of an exchange case example. MML, Medical markup language.

Data transformation

There are differences in the MML standard between the Japanese and Chinese versions,[44 45] and, even in Japan, the clinical data formats in individual iDolphin are dissimilar from each other. For example, Haniwa Net in Miyazaki uses MML 2.3 and Maiko Net in Kyoto uses MML 3.0. Moreover, there are other heterogeneous systems, including other EHRs and EMRs. To achieve data exchange between disparate systems, Global Dolphin has to implement a data transformation step in the clinical data exchange process to map the medical record structurally.

In this project, the InterSystems Ensemble platform[53] was used to design and develop the process of data transformation. Ensemble has a graphical mapping tool, which allows the user to 'draw' lines from fields in one set of data to fields in another. Once the MML file is uploaded to the system, it is captured and delivered in a universal, abstract format as a message object to the data transformation tool. The message consists of a header and a body object. According to the message routing rules and transformation rules, the adapter automatically chooses a mapping style to transform the message body object into a new one in order to fit the target format; through the format-free zone developed on Ensemble, heterogeneous systems can communicate with each other in a consistently compact, efficient, and streamlined manner.

We developed two sets of transformation rules in this project: one is for mapping different MML versions and the other is for mapping MML and HL7. Figure 3 shows an instance of data mapping from MML to our Chinese-localized EMR system (which has an HL7 interface) using the Ensemble tool.

Translation

Clinical information exchange between different countries must overcome a language barrier; this is the biggest difference from domestic health information exchange, and an issue that cannot be solved by medical industry standards or data transformation only. In the Global Dolphin system, the MML content is divided into three types, which are discussed below: the structured record, the free text-type phrase, and the free text-type paragraph.

1. For the structured record, we analyzed the terms and writing patterns of health information documents. Most of the

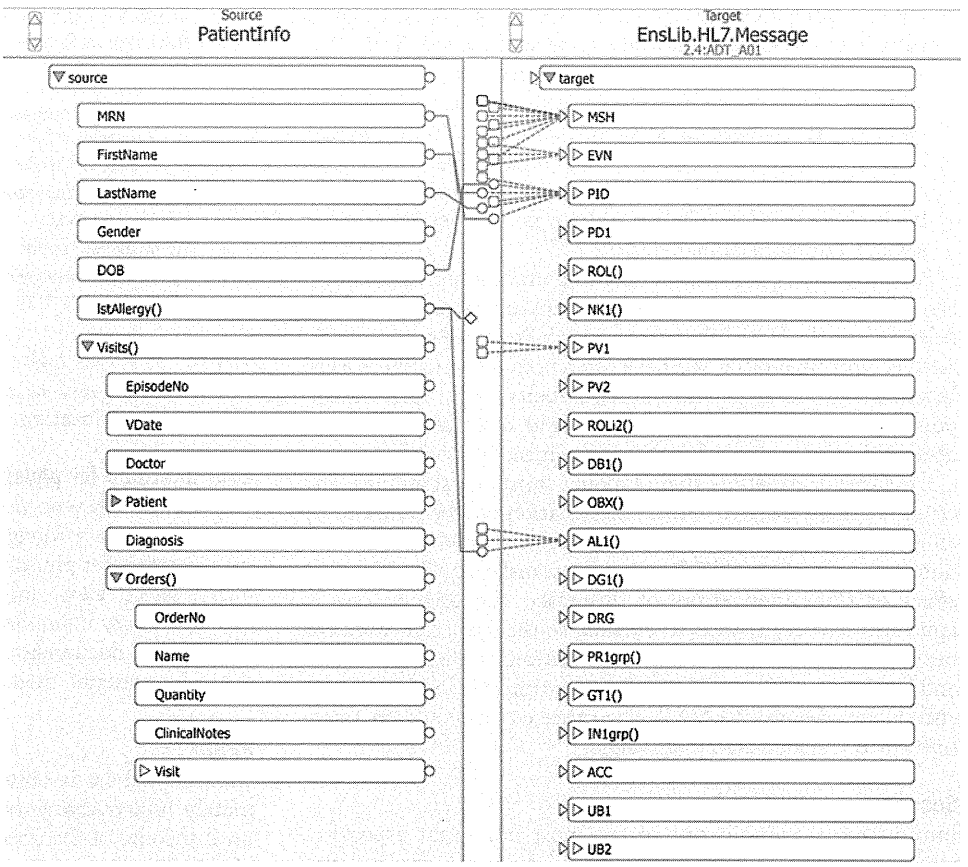

Figure 3 An example of data transformation using the Ensemble tool.

words recorded are medical terminology, such as disease names, and medical symbols that conform to standards, such as SNOMED, ICD10, and LOINC. For this type of record, a terminology-mapping table was established so that a data transformation method could be used to change the words from the source language to the destination language. Many medical terms in the documents are followed by an attribute or subordination enclosed in parentheses. For example, TP in 'syphilis (TP)' represents the TP test for syphilis. These attributes or subordinations are organized into a subclass column of each term for rapid mapping. In this way, the structured record can be automatically translated, and a new language can easily be added. Figure 4 shows a segment of the terminology-mapping table.

2. For the free text-type phrase, as it is written in natural language, the utilization of terminology mapping and replacement methods is impossible. However, the phrases are short and do not contain complicated grammar or medical terms, which means that they can be translated fairly accurately by translation software. In our project, the Google Language API[54] was adopted to automatically translate the short phrases. While the MML file is parsed, the elements of a free text-type phrase, such as '<Department> Second Department of Internal Medicine (Outpatient) </Department>', are marked, and the content is transferred as a parameter to the Google Language API to acquire the destination language.
3. The free text-type paragraph cannot be translated by a machine and requires human translation. The system extracts free text from the MML file and publishes it anonymously through a web interface for the translators of a third party to perform the manual translation work (see

Figure 4 A segment of the terminology mapping table.

PC-20090513...pping_table | 摘要

SN	Chinese	Subclass_cn	English	Subclass_en	Japanese	Subclass_jp
09.10	高血压	NULL	hypertension	NULL	高血圧	NULL
09.10.01	NULL	(自发性)	NULL	(essential)	NULL	(本態性)
09.10.02	NULL	(原发性)	NULL	(primary)	NULL	(原発性)
09.10.03	NULL	(动脉性)	NULL	(arterial)	NULL	(動脈性)
09.10.04	NULL	(良性)	NULL	(benign)	NULL	(良性)
09.10.05	NULL	(恶性)	NULL	(malignant)	NULL	(悪性)
09.10.06	NULL	(全身性)	NULL	(systemic)	NULL	(全身性)
09.11	高血压性心脏病	NULL	hypertensive heart disease	NULL	高血圧性心疾患	NULL
09.12	高血压性心脏衰竭	NULL	hypertensive heart failure	NULL	高血圧性心不全	NULL
09.13	动脉硬化性肾炎	NULL	arteriosclerotic nephritis	NULL	動脈硬化性腎炎	NULL
09.13.01	NULL	(慢性)	NULL	(chronic)	NULL	(慢性)
09.13.02	NULL	(间质性)	NULL	(interstitial)	NULL	(間質性)
*	NULL	NULL	NULL	NULL	NULL	NULL

online supplementary figure 2). Once the translation is submitted, it is automatically appended to the MML file, and users can see the complete information in their own language. Because the translation work is not performed in real time, the patient must submit an application to prepare his/her clinical information before he/she goes to another country. The third-party translators we use in our work have medical domain knowledge, and are not ad hoc translators, such as family or bilingual staff.[55 56]

Patient privacy protection is very important when the free text is sent out for translation. However, China and Japan do not have rules such as the Health Insurance Portability and Accountability Act yet. In this project, we have referenced some of the Health Insurance Portability and Accountability Act rules about protected health information (PHI) and a pattern matching deidentification means of protecting personal privacy.[57]

Language translation may produce misunderstandings and errors, so the translated clinical information will be followed by an icon, which indicates the translation method—that is, '!' for human translation and '?' for machine translation. To reduce the effect of translation errors of diagnoses, the original text is appended to every translated portion, so the users can check the health information themselves. In addition, to display Chinese and Japanese text on-screen at the same time, we use Unicode to encode and decode the MML file; other codes would be transformed to Unicode before exchange.

Security

Information security is one of the most important aspects in international clinical data exchange.[58 59] We ensure data security during access, transmission, and storage by the means described below.

A security gateway is set up between the internet and local area networks to separate the applications and database from the external network, preventing outside visitors from directly accessing the internal server. The gateway server is equipped with reverse proxy and a secure socket layer (SSL) virtual private network (VPN), and users need a digital certificate issued by the center to acquire access rights to the applications. Before a user executes a function, the access control list will check whether the user is permitted to perform that operation. In this way, the system can make sure that the right person performs the correct operation at the correct time.

When health information is transmitted via the internet, there is the possibility that it could be stolen and decrypted. Therefore documents transmitted via the internet are encrypted with a digital signature on the SSL VPN gateway, so that only the target user can decode the file stream and obtain a meaningful document.

The safety and authenticity of the data stored in the center is very important; a data backup and authenticity protection application was developed and installed to accomplish this goal based on our previously published work.[60–62]

Image data interoperability

Only the minimum necessary data will be stored in the regional clinical information center—for instance, a CT image will be uploaded to the data center only if it is attached to a CT report file, and additional images will remain in the PACS. We developed a service-oriented architecture-based interoperable image data application to enable access to the PACS in hospitals through a gateway server.[63] When users need more images beyond the storage of the regional center, they can access images from a PACS through a simple object-access protocol-based web service, and the regional center plays a role in certification authentication and access control, in addition to forwarding the request to the location of the image access service.

Table 1 Document numbers of the Xizi Regional Clinical Information Center up until the end of October 2010

Document type	Total amount
No of patient information records (unique number of patients)	245 000
No of diagnosis records	402 000
No of examination reports	188 000
No of test reports	351 000
No of surgery records	35 000
No of clinical summaries	61 000

User interface for physicians

The main users who need to access the clinical information of a patient from a foreign country are medical professionals. A user interface for physicians is provided in the center for them to query, select, view, and write the medical records (see online supplementary figure 3A–D). Accordingly, physicians can make new clinical documents, using free text or structured types, and can view patients' medical images from remote hospitals.

RESULTS

Currently, there is only one local hospital (660 beds, approximately 1000 outpatients daily) connected to the XRCIC, and, up until the end of October 2010, the XRCIC had collected a total of 245 000 Master Patient Index accounts from the hospital dating back to December 26, 2000, which made information on these patients available to the Global Dolphin system. Other detailed information for the last decade is listed in table 1.

In Japan, the scale of each regional project in Miyazaki and Kyoto is shown in table 2. Registered medical institutions in each region include one large general hospital and other small practices, most of which are private-physician practices. Almost all of the uploaded medical records were collected from the large general hospital in each region, Miyazaki University Hospital (612 beds, approximately 700 outpatients daily) and Kyoto University Hospital (1182 beds, approximately 3600 outpatients daily). The center has only the minimum necessary clinical data in its own database, including MML documents (text) and binary files attached to the MML documents (images).

We have exchanged the clinical data of 39 test patients from Japan to China for study, nine of whom had applied for a global ID. A total of 1153 documents were exchanged, including 1001 MML files and 152 images. Of the 1001 MML files, 197 were free text-type paragraphs that needed to be translated, and 103 of these paragraphs contained a total of 153 instances of PHI; the deidentification tool masked 90.2% of the PHIs in all of the texts; nine dates, three locations, and three names were missed.

At present, the state of our work is between a pilot study and a live application. Although there are no actual patient overlaps,

Table 2 Scale of each local project in Japan

	Miyazaki	Kyoto
Registered medical institutions	84	5
Uploaded medical records (unique number of patients)	384 000	237 000
No of documents sent (text)	1 600 000	7 000 000
No of documents sent (images)	85 000	86 000
Year started	2002	2007

the Global Dolphin is currently linked with the three regional information centers, and is on standby whenever someone needs it.

DISCUSSION AND CONCLUSION

Health information exchange has been identified as an essential strategy for addressing the crisis of cost, quality, and safety in healthcare all over the world.[51] However, there are four common barriers that hinder the implementation of clinical data exchange, which are widely agreed upon around the globe: communication, standardization, funding, and interoperability.[8] These barriers include both technical and non-technical aspects. As a result, most clinical data exchange occurs between organizations within a regional level, with some exchanges occurring at a national level. In Global Dolphin, we have designed and developed an international clinical data exchange system with several key applications and infrastructure that are technically ready for the sharing of health information among different countries.

Flexibility and expandability

The three-level configuration of the Dolphin Project is loosely coupled with other systems on the same level and between each of the levels, which makes it easy to incorporate a new system or level to update the existing system, as well as to communicate with other heterogeneous systems.

Modularity and reusability

All of the applications in Global Dolphin are modularized and encapsulated as services that can be easily reused and transformed into service-oriented architecture, so that system interoperability can also be achieved.

Consistency and continuity

The Global Dolphin system makes the exchange of health information available at the international level, keeps the health information of patients consistent, and improves medical services and the continuity of healthcare.

However, to assure that the Global Dolphin system works in practice, we have to consider more than merely technical aspects. For instance, the different standards for protecting privacy between countries could cause problems, eg, a patient's information in China may not be as well protected as in Japan; Global Dolphin system will always try to conform to the stricter privacy protection standards. In addition, some Chinese medical expressions and clinical sections either do not exist in Japan, or differ from those in Japan, including race, traditional Chinese clinics, traditional Chinese diagnosis category, etc. Furthermore, the Chinese health insurance system is also markedly different from that of Japan. Thus we have to adjust to these differences in work flow and modify the health insurance information module in order to make the exchanged data useful and understandable for each area.

Because of the international approach, we also have to consider health insurance coverage when we develop contracts. Normally, local health insurance is unavailable in most hospitals across borders. However, in our project, the local hospital we have chosen is approved by many multinational health insurance companies.

Although Global Dolphin has many advantages, some limitations are inevitable. The translation of free text-type paragraphs cannot be completed automatically; in our study cases, it usually took 1 day to finish the translation, which would become a severe issue in cases where the document is required immediately. In addition, an inaccurate translation could cause risk, especially when it concerns hypersensitivity. Furthermore, when the free text is translated by a third party, there is the possibility that the patient's identity could be inferred from the PHI missed or information other than the PHI. A further study on natural-language processing and a semantic-based deidentification method will be carried out and will hopefully resolve the above issues.

Global Dolphin provides an efficient way of dealing with syntax and structural interoperability in the exchange of clinical information, but system interoperability consists of more than data structure and sequencing information; the upper level of syntax is semantic interoperability.[64–66] In the future, more semantic interoperability technologies, such as ontology language, will be studied and incorporated into the system. For instance, we anticipate using semantic interoperability technologies to match a patient who does not have any IDs in our system.

According to the 39 study cases tested, most of the clinical data exchange in our work was largely within the same technical system (Dolphin Project) and used an MML standard. However, we have developed an HL7 interface based on Ensemble and can communicate with HL7-compatible systems (ie, the hospital connected to the XRCIC). In the future, we will link disparate systems to evaluated data exchange across institutions.

Global Dolphin is a trial of international clinical data exchange, and, as our work continues, we hope it will finally achieve the goal of facilitating access to, and retrieval of, clinical data to provide safer, more timely, efficient, effective, and equitable patient-centered care. Moreover, with the global accessibility of clinical data, many value-added services can be offered by the system in the future, such as international epidemic control, public health assessment, translational medicine research, and medical tourism.[67 68]

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Design and development of an international clinical data exchange system: the international layer function of the Dolphin Project

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Controlled-Release Basic Fibroblast Growth Factor for Peripheral Artery Disease: Comparison with Autologous Bone Marrow-Derived Stem Cell Transfer

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Objective: We examined the safety and efficacy of controlled-release basic fibroblast growth factor (b-FGF) for peripheral artery disease (PAD), compared with autologous bone marrow mononuclear cell implantation (BMCI).
Background: We recently developed a b-FGF-incorporated biodegradable hydrogel that enables slow-releasing drug delivery system.
Methods: PAD patients were divided into a b-FGF group ($n=10$) and BMCI group ($n=15$). Injection of gelatin hydrogel containing 600 μg b-FGF or BMCI ($0.4–5.1\times10^{10}$ cell) was performed. Visual analog pain scale (VAS), ^{99m}technetium-tetrofosmin (Tc-TF) scintigraphy, transcutaneous oxygen tension ($TcPO_2$), and ankle-brachial index (ABI) were evaluated before and 4 weeks after each treatment, and 2-year prognosis was determined.
Results: VAS (b-FGF 67±15 to 4±5, $p<0.01$, BMCI 67±42 to 5±9 mm, $p<0.01$) and $TcPO_2$ (b-FGF 16±14 to 47±17, $p<0.01$, BMCI 13±13 to 37±21 mmHg, $p<0.01$) were significantly improved in both groups. Tc-TF and ABI were not changed. Prognosis was similar between the groups (b-FGF 91%, BMCI 80%, NS).
Conclusion: Controlled-release b-FGF is as safe as BMCI, and its efficacy appears to be comparable. Thus, this therapy may be an alternative to BMCI.

Introduction

The development of new vessels from an existing network of vessels, a process referred to as angiogenesis, contributes to various pathological processes such as tumor progression and chronic inflammation.[1–3] On the other hand, neovascularization (angiogenesis) in response to ischemia is a desirable response against tissue hypoxia.[4–7] Therapeutic angiogenesis is a promising strategy for the treatment of many occlusive vascular diseases, such as myocardial and limb ischemia. To date, clinical studies on promoting angiogenesis in ischemic tissues have focused exclusively on the use of angiogenic growth factors, delivered using two main strategies.[8,9] One strategy has been to deliver recombinant proteins directly to the ischemic tissue by intramuscular or intraarterial injection. The alternate strategy has been to use gene therapy, by direct transfer of expression vectors with either virus or naked plasmid. An optimal delivery strategy has not been established, and the approach of using a large amount of protein or gene as a therapeutic agent has several disadvantages. Also, the outcome of early-phase clinical trials with a particular molecule has been less than encouraging, possibly because of factors such as selection and formulation of the growth factor, duration of exposure, route of administration, and selection of patients.[8,9] A cell-based approach, such as autologous bone marrow mononuclear cell implantation (BMCI), has more potential because bone marrow secretes variable cytokines in response to ischemia[10,11] and promotes angiogenesis.[12] However, in this cell-based therapy, it is difficult to standardize the amount, quality, and purification of cells, because the patients (cell donor) are not in identical condition. Also, it is difficult to confirm the type and amount of dominant angiogenic substance released from cells in the clinical situation.

Thus, to establish therapeutic regenerative medicine, there remains a clear need for research on an effective approach and the precise mechanisms by which to establish therapeutic angiogenesis. Recently, Tabata *et al.* designed a novel approach with a drug-delivery system (DDS) that enabled controlled release of a single growth factor *in vivo* and thus improved efficacy of growth factor therapy.[13] This DDS was

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incorporated with the potent growth factor, basic fibroblast growth factor (b-FGF), which has a strong angiogenic property and is a potent cytokine expressed in bone marrow in response to ischemia.[10,11] The present clinical study was designed to determine the effectiveness and safety of the use of a DDS-guided single angiogenic cytokine, b-FGF, which improved above disadvantage, for peripheral artery disease (PAD), and to confirm the mechanisms and whether a single cytokine can possess angiogenic property or not. In addition, the effect was compared with that of cell-based therapy utilizing BMCI.[14]

Methods

Patients

From April 2005 to May 2008, we enrolled 28 consecutive patients with arteriosclerosis obliterans or Buerger's disease with Fontaine class 3 or 4, aged 27–73 years. All the patients were indicated as limb amputation at previous hospital before visit to Nippon Medical School. With the approval of the ethics committee of Nippon Medical School, written informed consent was obtained from each patient. The advisory committee (consisting of cardiologists, vascular/plastic surgeons, radiologists, and an anesthesiologist) reviewed these patients, and 25 of them were selected as having no indication for vascular surgery or peripheral catheter intervention. Administration of the b-FGF into the muscle is off-label use; thus, we avoid other technical or hemodinamics affects to single-dose therapy. According to this concern, all of the patients who require surgical debridement or who on hemodialysis are allocated to BMCI group. The remaining patients were allocated to b-FGF group, which is not a randomized trial. Because patient selection is condition based, this study was not performed using sample size power analysis. Also, the procedures were totally different between treatments, and open label study was selected: 10 patients were allocated to b-FGF treatment and 15 to BMCI. Because these patients' condition was determined as severe limb ischemia requiring limb amputation, it was not possible to include control subjects from the ethics standpoint. Also, because the aim of this study was observation of the safety and efficacy of b-FGF therapy, patients who required additional interventions such as surgical treatment (including minor debridement or skingrafting) or who were treated with hemodialysis (which may affect hemodynamics) were allocated to the BMCI group. Exclusion criteria were (1) no evidence of angiological stenosis confirmed by digital subtraction angiography, (2) history of vascular surgery (within 30 days), (3) presence of any malignant disease or history of its treatment within 5 years (determined by fiberscopy, tumor marker, or fecal occult blood), (4) untreated proliferative diabetic retinopathy, (5) smoker unable to quit smoking, (6) drug addiction of any kind (including alcohol), (7) evidence of viral infection (HBV, HCV, and HIV), (8) infectious osteomyelitis, and (9) complication of any serious disease affecting the patient's general condition (heart, lung, kidney, or liver failure) (Fig. 1).

Endpoints

The primary endpoint of this project was the occurrence of an adverse event, such as death, life-threatening state, functional disturbance, or other severe condition. Secondary endpoints were pain relief, ulcer healing, and avoidance of amputation at 4 weeks' follow-up.

b-FGF therapy

Gelatin hydrogel microspheres (20 μm in diameter) incorporating b-FGF (Kaken Pharmaceutical) were prepared according to the method previously reported.[15–17] Briefly, 600 μg human recombinant b-FGF with an isoelectric point of 9.6 was mixed with hydrogel microspheres with an isoelectric point of 5.0 prepared from bovine gelatin (Nitta Gelatin) through an alkaline process. Gelatin microspheres incorporating b-FGF can release b-FGF for 2–3 weeks.[17] Microspheres were carefully prepared under clean conditions. To confirm the safety of gelatin microspheres, culture test and endotoxin level were examined according to the Japanese Pharmacopoeia regulations and found to be negative. To maintain enough local concentration in the tissue, gelatin

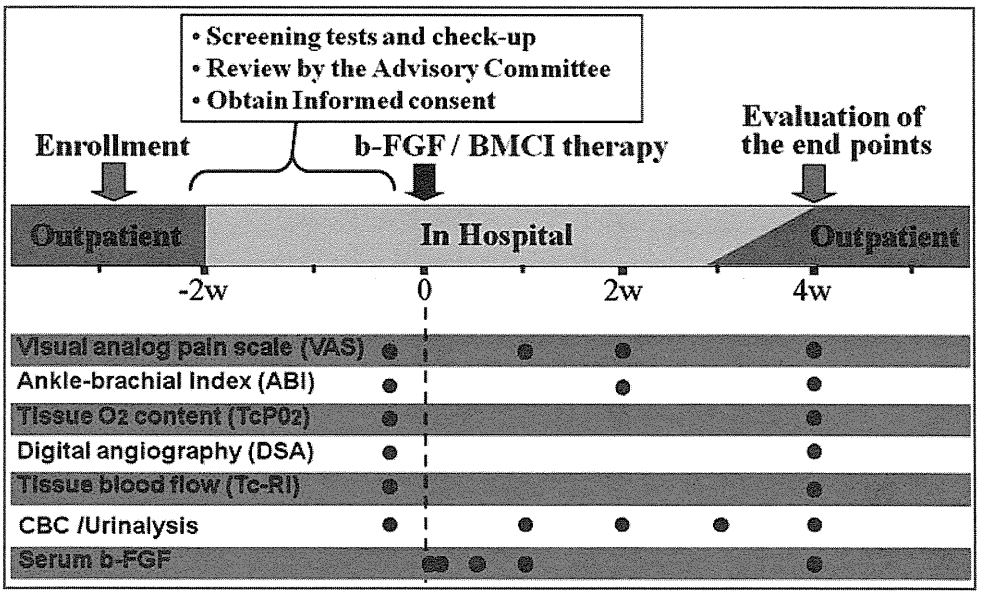

FIG. 1. Study schedule. VAS, visual analog pain scale; ABI, ankle-brachial index; DSA, digital subtraction angiography; Tc-RI, ^{99m}Technetium tetrofosmin scintigraphy; CBC, complete blood count; b-FGF, controlled-release basic fibroblast growth factor therapy; BMCI, bone marrow mononuclear cell implantation; $TcPO_2$, transcutaneous oxygen tension.

hydrogel microspheres incorporating b-FGF were dispersed in 20 mL saline. To avoid local edema associated with injected fluid, injection amount was standardized as 1 mL/site. Based on the ultrasound procedure, 20 sites to be injected were pre-determined with reference to the vasculature of the calf muscles, and marked in advance. Echo-guided intramuscular direct injection (1 mL/site) was performed on calf and foot muscles under general or epidural anesthesia.

BMCI therapy

This method was described previously.[14] Briefly, bone marrow (400–600 mL, 2.6–6.5×10^9 cells in total) was collected from the bilateral iliac bones under general anesthesia. The mononuclear cell fraction was sorted, and 60–100 mL of cell suspension was processed by a cell separator (AS-TEC 204; Fresenius). Injection points were marked beforehand using transparent sheets with a 3×3 cm grid. To avoid local edema associated with injected fluid, injection amount was standardized as 1 mL/site as mentioned above. Thus, total point for intramuscular injection was about 70 points/leg.

Examinations

The following parameters were evaluated. Pain scale (visual analog pain scale [VAS]), which indicated maximum pain as 100 mm and minimum as 0 (Ankle-brachial index [ABI]; Omron Healthcare) (Fig. 1). ABI was measured by standard methods, and calculated as the ratio of the ankle to brachial pressure. Tissue oxygen content was measured by TCM 400 (transcutaneous oxygen tension [$TcPO_2$]; Radiometer). The sampling site was cleaned with alcohol. The positioning did not overlie a bony prominence, superficial vessel, or pulse site. Then, the transducer was placed on the dorsum of the ischemic limb, and warmed up to 43.5°C to increase the permeability of the skin to oxygen molecules at the measurement site. With the patients resting in supine position, data were acquired in room air for about 20 min. Digital subtraction angiography was performed using the standard technique with 4F catheter. Tissue blood flow was determined by ^{99m}technetium tetrofosmin (^{99m}Tc-TF) scintigraphy.[14] ^{99m}Tc-TF (555–740 MBq) was injected intravenously. Approximately 10 min after injection of the radiotracer, whole-body scintigraphy was performed in the prone position both in the anterior and posterior projection with a dual-head large field-of-view gamma camera (Vertex, ADAC). Image acquisition time was approximately 15 min. For quantitative analysis, regions of interest of equal size were drawn around the appropriate muscle group (e.g., calf muscles) in anterior and posterior projections. Additionally, intra cranial uptake (brain uptake) was calculated as the background. The muscle-to-brain ratio was defined as average counts per pixel in each muscle/average counts per pixel in the brain. Evaluation was performed before and 4 weeks after therapy.

TABLE 1. STUDY PATIENT POPULATION

	b-FGF (n=10)	*BMCI (n=15)*
Age	53±17	61±13
Male	10 (100%)	13 (87%)
Fontaine classification	3.6±0.5	3.9±0.3[a]
ASO/Buerger disease	6/4	12/3
Previous smoker	9 (90%)	9 (60%)
Diabetes mellitus	5 (50%)	10 (67%)

[a] $p < 0.05$.
ASO, arteriosclerosis obliterance; b-FGF, basic fibroblast growth factor; BMCI, bone marrow mononuclear cell implantation.

Safety evaluation

To evaluate the possible side effects of b-FGF, blood concentration was measured immediately after injection, 1 day, 1 week, 2 weeks, and 4 weeks after administration. Also, urinalysis was performed at 3 days, 1 week, 2 weeks, and 4 weeks after administration. For the long-term prognosis analysis, Kaplan–Meier analysis was performed 2 years after administration.

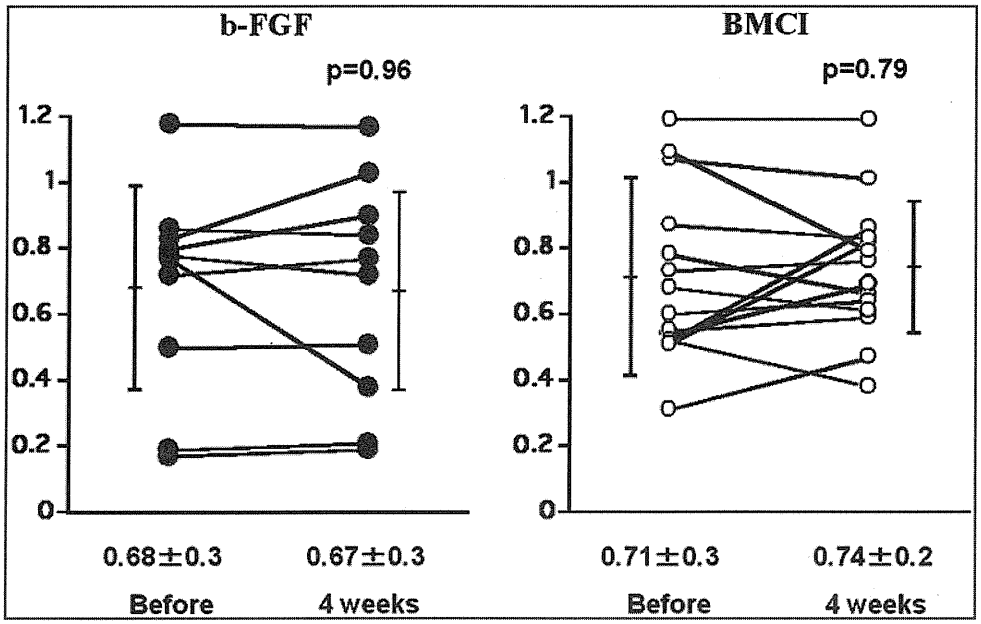

FIG. 2. The effect of controlled-release b-FGF therapy to ABI. b-FGF therapy (left) and BMCI therapy (right).

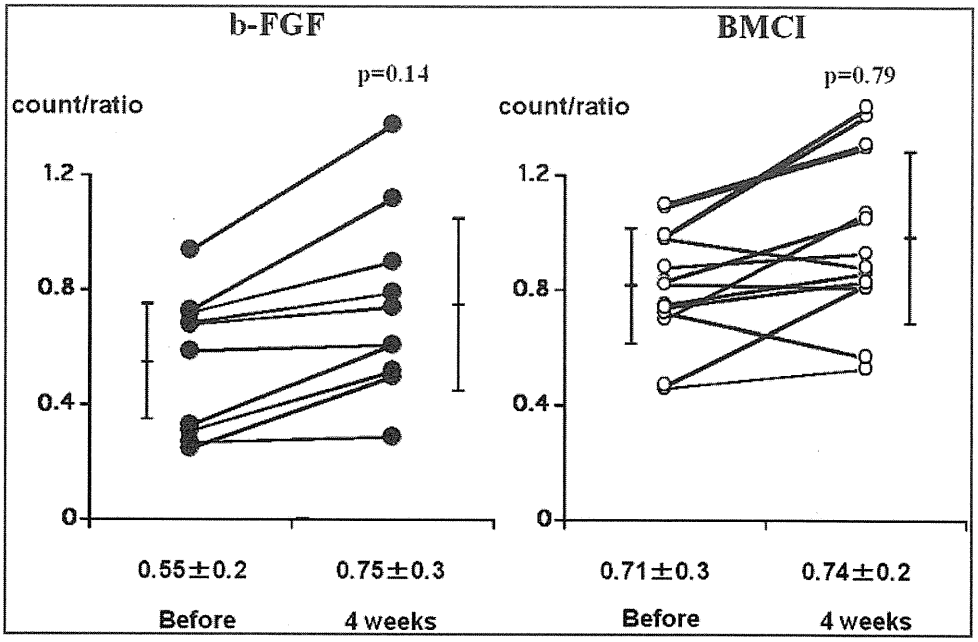

FIG. 3. The effect of controlled-release b-FGF therapy to ^{99m}Technetium-tetrofosmin scintigraphy. b-FGF therapy (left) and BMCI therapy (right).

Statistical analysis

All data are presented as mean±SD. Repeated measure analysis of variance was used to test for treatment-group baseline differences for continuous variables. Within-treatment analyses of changes were performed using a Student's *t*-test. Time to all cause mortality was compared between the two groups using Kaplan–Meier analysis with log-rank test. A value of $p<0.05$ was taken as the minimum level of significance.

Results

Baseline characteristics are shown in Table 1. Age, sex, original disease, smoking history, and diabetes mellitus prevalence were similar between two groups. Because all the patients with an ischemic ulcer requiring a skin graft or minor debridement were allocated to the BMCI group, Fontaine classification was worse in the BMCI group than in the b-FGF group. Regarding the primary end point, no adverse event occurred during the 4-week period in both groups. Also, no amputation was required during this period. Figure 2 shows the effect of therapy on ABI. ABI was not significantly increased 4 weeks after treatment in both groups (b-FGF 0.7±0.3 to 0.7±0.3, $p=0.96$, BMCI 0.7±0.3 to 0.7±0.2, $p=0.79$). ^{99m}Tc-TF scintigraphy was performed to evaluate tissue blood flow. There was a tendency for ^{99m}Tc-TF to increase in both groups; however, it did not reach statistical significance 4 weeks after treatment (b-FGF 0.5±0.2 to 0.8±0.2, $p=0.14$, BMCI 0.7±0.3 to 0.7±0.2 count ratio/pixel, $p=0.79$; Fig. 3). Figure 4 shows the time course of

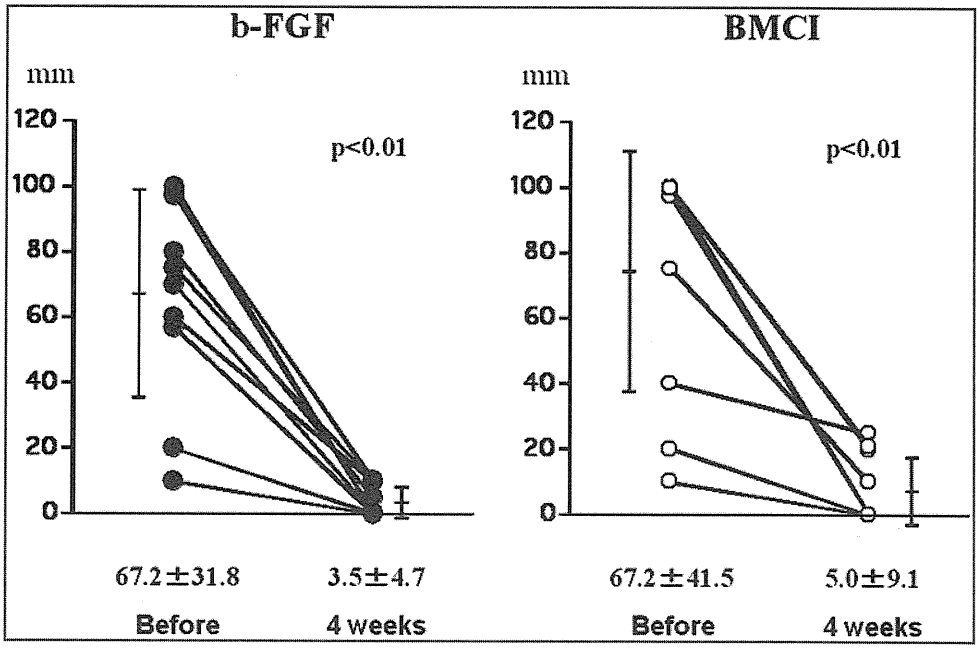

FIG. 4. The effect of controlled-release b-FGF therapy to pain scale (VAS). b-FGF therapy (left) and BMCI therapy (right).