

Balloon Kyphoplasty for Treatment of Painful Osteoporotic Vertebral Compression Fractures

An Evidence Update

*Presented to the Ontario Health Technology
Advisory Committee in June 2010*

October 2010



Medical Advisory Secretariat
Ministry of Health and Long-Term Care

About this Review

This review updates the following evidence-based analysis:

Medical Advisory Secretariat. Balloon kyphoplasty: an evidence-based analysis. Ont Health Technol Assess Series [Internet]. 2004 Dec; 4(12). 1-45. Available at:
http://www.health.gov.on.ca/english/providers/program/mas/tech/ohtas/tech_kypho_120104.html

Suggested Citation

This evidence update should be cited as follows:

Medical Advisory Secretariat. Balloon kyphoplasty for treatment of painful osteoporotic vertebral compression fractures: an evidence update. Ont Health Technol Assess Ser [Internet]. 2010 Sept [cited YYYY MM DD]; 10(20) 1-22. Available from:
http://www.health.gov.on.ca/english/providers/program/mas/tech/reviews/pdf/rev_kyphoplasty_osteo_20100930.pdf.

Permission Requests

All inquiries regarding permission to reproduce any content in the *Ontario Health Technology Assessment Series* should be directed to MASinfo.moh@ontario.ca.

How to Obtain Issues in the Ontario Health Technology Assessment Series

All reports in the *Ontario Health Technology Assessment Series* are freely available in PDF format at the following URL: www.health.gov.on.ca/ohtas. Print copies can be obtained by contacting MASinfo.moh@ontario.ca.

Conflict of Interest Statement

All analyses in the *Ontario Health Technology Assessment Series* are impartial and subject to a systematic evidence-based assessment process. There are no competing interests or conflicts of interest to declare.

Peer Review

All Medical Advisory Secretariat analyses are subject to external expert peer review. Additionally, the public consultation process is also available to individuals wishing to comment on an analysis prior to finalization. For more information, please visit
http://www.health.gov.on.ca/english/providers/program/ohtac/public_engage_overview.html.

Contact Information

The Medical Advisory Secretariat
Ministry of Health and Long-Term Care
20 Dundas Street West, 10th floor
Toronto, Ontario, CANADA
M5G 2C2
Email: MASinfo.moh@ontario.ca
Telephone: 416-314-1092
TTY: 1-877-512-4055

ISSN 1915-7398 (Online)
ISBN 978-1-4435-4235-7 (PDF)

About the Medical Advisory Secretariat

The Medical Advisory Secretariat is part of the Ontario Ministry of Health and Long-Term Care. The mandate of the Medical Advisory Secretariat is to provide evidence-based policy advice on the coordinated uptake of health services and new health technologies in Ontario to the Ministry of Health and Long-Term Care and to the healthcare system. The aim is to ensure that residents of Ontario have access to the best available new health technologies that will improve patient outcomes.

The Medical Advisory Secretariat also provides a secretariat function and evidence-based health technology policy analysis for review by the Ontario Health Technology Advisory Committee (OHTAC).

The Medical Advisory Secretariat conducts systematic reviews of scientific evidence and consultations with experts in the health care services community to produce the *Ontario Health Technology Assessment Series*.

About the Ontario Health Technology Assessment Series

To conduct its analyses, the Medical Advisory Secretariat reviews available scientific literature, collaborates with partners across relevant government branches, and consults with clinical and other external experts and manufacturers, and solicits any necessary advice to gather information. The Medical Advisory Secretariat makes every effort to ensure that all relevant research, nationally and internationally, is considered.

The information gathered is the foundation of the evidence to determine if a technology is effective and safe for use in a particular clinical population or setting. Information is collected to understand how a new technology fits within current practice and treatment alternatives. Details of the technology's diffusion into current practice and input from practising medical experts and industry add important information to the review of the provision and delivery of the health technology in Ontario. Information concerning the health benefits; economic and human resources; and ethical, regulatory, social and legal issues relating to the technology assist policy makers to make timely and relevant decisions to optimize patient outcomes.

If you are aware of any current additional evidence to inform an existing evidence-based analysis or evidence update, please contact the Medical Advisory Secretariat: MASinfo.moh@ontario.ca. The public consultation process is also available to individuals wishing to comment on an analysis prior to publication. For more information, please visit http://www.health.gov.on.ca/english/providers/program/ohdac/public_engage_overview.html.

Disclaimer

This evidence update was prepared by the Medical Advisory Secretariat, Ontario Ministry of Health and Long-Term Care, for the Ontario Health Technology Advisory Committee and developed from analysis, interpretation, and comparison of scientific research and/or technology assessments conducted by other organizations. It also incorporates, when available, Ontario data, and information provided by experts and applicants to the Medical Advisory Secretariat to inform the analysis. While every effort has been made to reflect all scientific research available, this document may not fully do so. Additionally, other relevant scientific findings may have been reported since completion of the review. This evidence-based analysis is current to the date of the literature review specified in the methods section. This analysis may be superseded by an updated publication on the same topic. Please check the Medical Advisory Secretariat Website for a list of all evidence-based analyses, updates, and related documents: <http://www.health.gov.on.ca/ohdas>.

Table of Contents

| | |
|---|-----------|
| LIST OF ABBREVIATIONS | 5 |
| OBJECTIVE | 6 |
| SUMMARY OF HEALTH TECHNOLOGY ASSESSMENT REPORT 2004 | 6 |
| Results of Literature Search | 6 |
| Summary of the Report | 6 |
| EVIDENCE-BASED ANALYSIS: UPDATE | 8 |
| Research Methods | 8 |
| Literature Search..... | 8 |
| <i>Search Strategy</i> | 8 |
| <i>Inclusion Criteria</i> | 8 |
| <i>Exclusion Criteria</i> | 8 |
| Statistical Analysis..... | 9 |
| Quality of Evidence..... | 9 |
| Quality of the Randomized Controlled Trials | 9 |
| Quality of Body of Evidence | 9 |
| Results of Evidence-Based Analysis | 10 |
| Results of Two Open Randomized Controlled Trials..... | 10 |
| Balloon Kyphoplasty versus Non-Surgical Care | 10 |
| Balloon Kyphoplasty Versus Vertebroplasty | 12 |
| Incidence of New Vertebral Fractures and Adverse Events..... | 13 |
| Quality of the Studies | 14 |
| Quality of Body of Evidence..... | 15 |
| Summary & Conclusion | 16 |
| GLOSSARY | 17 |
| Glossary for Scales used in RCTs on Balloon Kyphoplasty | 18 |
| APPENDICES | 19 |
| APPENDIX 1: LITERATURE SEARCH STRATEGIES | 19 |
| APPENDIX 2: GRADE OF EVIDENCE | 21 |
| REFERENCES | 22 |

List of Abbreviations

| | |
|--------------|--|
| BK | Balloon kyphoplasty |
| CI | Confidence interval |
| MAS | Medical Advisory Secretariat |
| MCID | Minimal clinically important difference |
| NSC | Non-surgical care |
| OHTAC | Ontario Health Technology Advisory Committee |
| RCT | Randomized controlled trial |
| SD | Standard deviation |
| VAS | Visual Analogue Scale |
| VCF | Vertebral compression fracture |
| VP | Vertebroplasty |

Objective

The objective of this report is to review the results of randomized controlled trials on balloon kyphoplasty as an update to the report produced in 2004 regarding efficacy and safety of balloon kyphoplasty for treatment of painful osteoporotic vertebral compression fractures (VCFs). (1)

Summary of Health Technology Assessment Report 2004

Results of Literature Search

No randomized controlled trials on balloon kyphoplasty were found in 2004. All of the published studies were case series without a control group. Eleven studies met the inclusion criteria from which 8 were in patients with osteoporosis. The remaining studies included some patients with multiple myeloma or metastatic disease. There was also a comparative study published in German that had been translated into English. The results of this study were also discussed in 2004 report. The results of the studies on patients with osteoporosis were discussed separately from those on patients with multiple myeloma or metastatic disease.

Summary of the Report

The case series reported on several important clinical outcomes.

Pain: Four studies on patients with osteoporosis and 1 study on patients with multiple myeloma/metastatic disease used the Visual Analogue Scale (VAS) to measure pain before and after balloon kyphoplasty. All of these studies reported that patients had significantly less pain after the procedure. This was maintained during follow-up. Two other studies on patients with osteoporosis also used the VAS to measure pain and found a significant improvement in pain scores; however, they did not provide follow-up data.

Vertebral body height: All 5 studies that assessed vertebral body height in patients with osteoporosis reported a significant improvement in vertebral body height after balloon kyphoplasty. One study had 1-year follow-up data for 26 patients. Vertebral body height was significantly better at 6 months and 1 year for both the anterior and midline measurements.

Two studies reported that vertebral body height was restored significantly after balloon kyphoplasty for patients with multiple myeloma or metastatic disease. In another study, the researchers reported complete height restoration in 9% of patients, a mean 56% height restoration in 60% of patients, and no appreciable height restoration in 31% of the patients who received balloon kyphoplasty.

Kyphosis correction: Four studies that assessed Cobb angle before and after balloon kyphoplasty in patients with osteoporosis found a significant reduction in degree of kyphosis after the procedure. In these studies, the differences between preoperative and postoperative Cobb angles were 3.4°, 7°, 8.8°, and 9.9°.

Only one study investigated kyphosis correction in patients with multiple myeloma or metastatic disease. The authors reported a significant improvement (5.2°) in local kyphosis.

Quality of life: Four studies used the Short Form 36 (SF-36) Health Survey Questionnaire to measure the

quality of life in patients with osteoporosis after they had balloon kyphoplasty. A significant improvement in most of the domains of the SF-36 (bodily pain, social functioning, vitality, physical functioning, mental health, and role functioning) was observed in 2 studies. One study found that general health declined, although not significantly, and another found that role emotional declined.

Two studies that used the Oswestry Disability Index found that patients had a better quality of life after balloon kyphoplasty. In one study, this improvement was statistically significant. In another study, researchers found that quality of life after kyphoplasty improved significantly, as measured with the Roland-Morris Disability Questionnaire. Yet another study used a quality of life questionnaire and found that 62% of the patients who had balloon kyphoplasty had returned to normal activities, whereas 2 patients had reduced mobility.

To measure quality of life in patients with multiple myeloma or metastatic disease, one group of researchers used the SF-36 and found significantly better scores on bodily pain, physical functioning, vitality, and social functioning after kyphoplasty. However, the scores for general health, mental health, role physical, and role emotional had not improved. A study that used the Oswestry Disability Index reported that patients' scores were better postoperatively and at 3 months follow-up.

One prospective German-language study was identified through the documentation provided for services of health insurance in one European country. The results of this study (level 3a evidence) showed that, compared with conservative medical care, balloon kyphoplasty significantly improved patient outcomes. Patients who had balloon kyphoplasty reported a significant reduction in pain that was maintained throughout follow-up (6 months), whereas pain scores did not change in the control group. Patients in the balloon kyphoplasty group did not need pain medication after 3 days. In the control group, about one-half of the patients needed more pain medication in the first 4 weeks after the procedure. After 6 weeks, 82% of the patients in the control group were still taking pain medication regularly. Adjacent fractures were more frequent in the control group than in the balloon kyphoplasty group.

These were the main findings on complications of balloon kyphoplasty in patients with osteoporotic VCFs:

- The bone cement leaked in 37 (6%) of 620 treated fractures.
- There were no reports of neurological deficits.
- There were no reports of pulmonary embolism due to cement leakage.
- There were 6 cases of cardiovascular events in 362 patients:
 - 3 (0.8%) patients had myocardial infarction.
 - 3 (0.8%) patients had cardiac arrhythmias.
- There was 1 (0.27%) case of pulmonary embolism due to deep venous thrombosis.
- There were 20 (8.4%) cases of new fractures in 238 patients.

For patients with multiple myeloma or metastatic disease, these were the main complications:

- The bone cement leaked in 12 (9.6%) of 125 procedures.
- There were no reports of neurological deficits.

Evidence-Based Analysis: Update

Research Methods

Literature Search

Search Strategy

A literature search was performed on Feb 9, 2010 using OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, EMBASE, the Cumulative Index to Nursing & Allied Health Literature (CINAHL), the Cochrane Library, and the International Agency for Health Technology Assessment (INAHTA) for studies published from January 1, 2005 to February 9, 2010. The search was updated on Aug 9, 2010 to ensure that no literature meeting the inclusion criteria had been published since the initial search date.

Studies were initially reviewed by titles and abstracts. For those studies meeting the eligibility criteria, full-text articles were obtained and reviewed. Reference lists were also examined for any additional relevant studies not identified through the search. Articles with an unknown eligibility were reviewed with a second clinical epidemiologist and then a group of epidemiologists until consensus was established. Data extraction was carried out by the author.

Inclusion Criteria

- Study design: Randomized controlled trials (RCTs) comparing balloon kyphoplasty with a control group or other interventions
- Study population: Adult patients with osteoporotic VCF
- Study sample size: Studies included 20 or more patients
- English language full-reports
- Published between Jan 1, 2005 and Aug 9, 2010

Exclusion Criteria

- Non-randomized studies
- Studies on conditions other than VCF (e.g. patients with multiple myeloma or metastatic tumors)
- Studies focused on surgical techniques
- Studies lacking outcome measures

Primary Outcome

- Changes in back-related pain scores

Secondary Outcomes

- Changes in scores related to disability (Physical functioning scores)
- Changes in scores related to mental and social functioning
- Incidence of new VCFs
- Incidence of cement leakage and subsequent neurological adverse events

Statistical Analysis

For comparison of scores, mean differences and 95% confidence intervals (CI) at the baseline and at different time points after the intervention were recorded and compared. The minimal clinically important difference (MCID) for various scores was identified through the literature and used as a tool to measure the degree to which the differences in scores are clinically important.

Quality of Evidence

Quality of the Randomized Controlled Trials

The Jadad instrument (2) was used to determine the quality of the RCTs on balloon kyphoplasty in terms of how they were designed and how they were conducted. This instrument is recommended by Cochrane Musculoskeletal Group in the preparation of their Cochrane systematic reviews, and is the only instrument that has been constructed according to psychometric principles. The Jadad scale uses a simple and easy to understand approach that incorporates the most important components of methodological quality; randomization, blinding, and handling of patient attrition. This instrument has been used extensively in musculoskeletal research. (3)

Quality of Body of Evidence

The quality of the body of evidence was assessed as high, moderate, low, or very low according to the GRADE Working Group criteria. (4) Four key elements of the GRADE system are study design, study quality, consistency, and directness. The description of the 4 elements is:

1. Study design refers to the basic design of the study and has broadly categorized as observational studies and randomized trials.
2. Quality refers to the detailed study method and execution. For RCTs, for example, adequacy of allocation, concealment, and blinding must be taken into account in determining the study quality.
3. Consistency refers to the similarity of estimates of effect across studies. If there are important and unexplained inconsistencies in the results, our confidence in the estimate of effect for that outcome decreases. Differences in the direction of effect, the size of the differences in effect, and the significance of the differences guide the decision about whether important inconsistency exists.
4. Directness refers to the extent to which the interventions and outcome measures are similar to those of interest. For example, there may be uncertainty about the directness of the evidence if people of interest are older or sicker than the study population.

As stated by the GRADE Working Group, the following definitions of quality were used in grading the quality of the evidence:

| | |
|-----------------|---|
| High | Further research is very unlikely to change confidence in the estimate of effect. |
| Moderate | Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate. |
| Low | Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate. |
| Very Low | Any estimate of effect is very uncertain |

Results of Evidence-Based Analysis

A systematic search yielded 221 citations (search strategy is available in Appendix 1). The titles and the abstracts of the citations were reviewed and full text of the identified citations was retrieved for further consideration. Upon review of the full publications and applying the inclusion and exclusion criteria, 2 RCTs were identified. (5;6) One study (6) compared balloon kyphoplasty with non-surgical care and one study (5) compared balloon kyphoplasty with vertebroplasty. (Table 1)

Table 1: Quality of Evidence of Included Studies (7)

| Study Design | Level of Evidence† | Number of Eligible Studies |
|---|--------------------|----------------------------|
| Large RCT, systematic review of RCTs | 1 | 2 |
| Large RCT unpublished but reported to an international scientific meeting | 1(g) | N/A |
| Small RCT | 2 | N/A |
| Small RCT unpublished but reported to an international scientific meeting | 2(g) | N/A |
| Non-RCT with contemporaneous controls | 3a | N/A |
| Non-RCT with historical controls | 3b | N/A |
| Non-RCT presented at international conference | 3(g) | N/A |
| Surveillance (database or register) | 4a | N/A |
| Case series (multisite) | 4b | N/A |
| Case series (single site) | 4c | N/A |
| Retrospective review, modelling | 4d | N/A |
| Case series presented at international conference | 4(g) | N/A |
| | Total | 2 |

RCT refers to randomized controlled trial;

Results of Two Open Randomized Controlled Trials

Balloon Kyphoplasty Versus Non-Surgical Care

The Fracture Reduction Evaluation [FREE] trial (6) was conducted at 21 sites in 8 countries between February 2003 and December 2005. The study was funded by Medtronic Spine LLC. A total of 1,279 patients were assessed for eligibility, from which 655 did not meet the inclusion criteria, 209 refused to participate, and 115 had other reasons for exclusion. A total of 300 patients with painful VCFs were included in the study and were randomly assigned to balloon kyphoplasty (n=149) or non-surgical care (n=151). The study had an 80% power to detect 0.5 SD for the one month difference in change for the SF-36 Physical Component Summary (PCS) scores based on the two-sided type 1 error of 5%.

Inclusion criteria were:

- Patients who had 1-3 painful VCFs from T5 through L5
- Patients with VCFs due to osteopenia arising from primary or secondary osteoporosis, multiple myeloma, or osteolytic metastatic tumors

- Back pain score of 4 or more on a 0-10 point scale
- At least one fracture showing edema on MRI
- At least one fracture having a 15% loss of height

Exclusion criteria were:

- Age < 21 years
- Chronic fractures (> 3 months)
- Pedicle fracture
- Previous vertebroplasty
- Neurological deficit
- Radicular pain
- Spinal cord compression or canal narrowing
- Patients taking unintermittent anticoagulation therapy
- Patients with known allergy to kyphoplasty materials or contraindications to MRI
- Dementia
- Unable to walk before fracture (walking aids were allowed)
- VCF due to primary bone tumour, osteoblastic metastases, or high energy trauma

Two patients in each group had VCF due to multiple myeloma or tumour metastasis. The mean age of the fracture was 5.6 weeks (SD 4.4) in the kyphoplasty group and 6.4 weeks (SD 5.2) in the non-surgical care group. The primary end point of the study was the change in the SF-36 PCS scores from baseline to one month. The secondary outcomes were SF-36 subscales, European Quality of Life-5 Dimensions (EQ-5D), self-reported back pain on a scale from 0 to 10, Roland-Morris Disability Questionnaire (RDQ), and restricted activity days and bed rest because of back pain during the previous 14 days.

FREE was an open trial in which patients and outcome assessors were not blinded to the treatment assignment. Patients in the non-surgical care group received usual care according to the practices of participating centres; therefore the treatment methods were not standardized. From 149 patients who were assigned to the balloon kyphoplasty group, 11 did not complete one month follow-up. This included 10 patients who did not receive the procedure and one who had dementia. From 151 patients who were assigned to the non-surgical care group, 23 did not complete one month follow-up. Nine of these patients withdrew and underwent surgery. An additional 4 patients in the kyphoplasty group and 11 patients in the non-surgical care treatment group did not complete 3 months follow-up. Six months and 12 months follow-ups were completed by 131 and 124 patients in the kyphoplasty group and 115 and 111 patients in non-surgical care group respectively. Repeated measures analysis of variance with mixed models was used to include all 300 patients in the analysis. The results were analyzed by intention to treat.

At one month, the mean score for SF-36 PCS was 5.2 points higher than the non-surgical care group (95% CI, 2.9 to 7.4, $P < .0001$). The mean difference between the two groups at 3, 6, and 12 months were 4 point (95% CI, 1.6-6.3, $P < .0001$), 3.2 points (95% CI, 0.9-5.6, $P = .0064$), and 1.5 points (95% CI, -0.8 to 3.9, $P = .2$) respectively.

Pain scores, which was the primary end point of this health technology assessment, at the baseline and shorter follow-ups were not reported by the FREE trial. At one week a decrease of 2.2 points (95% CI, 1.6-2.8) more in the kyphoplasty group than in non-surgical care group was observed ($P < .0001$). At 12 months, the difference in pain scores was 0.9 points (0.3-1.5), $P = .0034$. The difference in scores between 1 week and 12 months are not reported by numbers but a Graph has been provided. According to the Graph, pain scores also decreased over time in the non-surgical care group (approximately from 7 at the baseline to 4.5 at 3 months). The graph in respect to the difference in taking opioid drugs was presented along with respective p-values which showed a significant difference in opioids use at 1 month,

3 months, and 6 months after the intervention favouring kyphoplasty. Scores for several subscales of SF-36 improved more in kyphoplasty than non-surgical care group but the results were reported as averaged across 12 months.

Balloon Kyphoplasty Versus Vertebroplasty

Liu et al. (5) conducted a randomized clinical trial to investigate the effectiveness of vertebroplasty versus balloon kyphoplasty. One hundred patients with osteoporotic VCFs at the thoracolumbar (T12-L1) vertebra were randomly assigned into two groups: vertebroplasty (50) and kyphoplasty (50). Block randomization technique was used. The mean age of the patients was 74.3±6.4 (range, 57-88) in the vertebroplasty group and 72.3±7.6 (range, 57-84) in the kyphoplasty group. Both procedures were performed within 43 days after injury (acute and subacute fractures). The mean duration between injury and surgery was 15.8±6.7 days for vertebroplasty and 17±7.7 days for balloon kyphoplasty. Patients in the two groups did not differ significantly in age, gender, location of VCFs, duration between injury and surgery, pre-operative pain scores, vertebral body height, or kyphotic wedge angle.

Measurements of pain on a 10-point visual analogue scale, and kyphotic wedge angle (to evaluate kyphosis) were made before and after surgery. The minimum follow-up period was 6 months.

The operation time for the kyphoplasty group was longer than the vertebroplasty group (46.2±4.5 min vs. 44±4.4 min, P < .05). The amount of injected bone cement was also greater in kyphoplasty than vertebroplasty (5.56±0.62 ml, vs. 4.91±0.65 ml, P < .001).

The pain scores in the kyphoplasty group decreased from 8±0.8 at the baseline to 2.6±0.6 at 3 days after surgery (P < .001) and remained constant until the final follow-up at 6 months. Similarly, the pain score in the vertebroplasty group decreased from 7.9±0.7 at the baseline to 2.3±0.5 at 3 days (P < .001) and it was 2.6±0.6 at 6 months follow-up. The study did not find any statistical significance difference between the two treatment groups at any time period examined.

In this study both kyphoplasty and vertebroplasty resulted in significant increase in vertebral body height and significant reduction in kyphotic wedge angle. However, these measures were significantly greater with kyphoplasty compared to vertebroplasty (P < .001)

In the kyphoplasty group, the vertebral body height increased from 1.13±0.34 cm to 2.04±0.41 cm (P < .001). In the vertebroplasty group, this measure increased from 1.01±0.22 cm to 1.32±0.26 cm (P < .001). The post operative kyphotic wedge angle in the kyphoplasty group was 9±5.7 and it was 12.2±3.6 in the vertebroplasty group; P < .001. (Table 2)

Table 2. Vertebral Body height and Kyphotic Wedge Angle: Balloon Kyphoplasty Versus Vertebroplasty (5)

| Procedure | Vertebral Body Height Cm | Kyphotic Wedge Angle Degree |
|--|--|--|
| Balloon kyphoplasty | Baseline: 1.13±0.34 Post-procedure: 2.04±0.41 P < .001 | Baseline: 17±7.3 Post-procedure: 9±5.7 P < .001 |
| Vertebroplasty | Baseline: 1.01±0.22 Post-procedure: 1.32±0.26 P < .001 | Baseline: 15.5±4.2 Post-procedure: 12.2±3.6 P < .001 |
| Balloon kyphoplasty vs. vertebroplasty | P < .001* | P < .001* |

* In favor of balloon kyphoplasty

Two patients in the kyphoplasty group developed new adjacent VCFs; one at 41 days and one at 50 days after the procedure.

Table 3 shows scores for pain and Table 4 shows scores for SF-36 (PCS), RDQ, and EQ-5D reported by the two RCTs.

Table 3. Mean Pain Scores After Intervention: Randomized Controlled Trials of Balloon Kyphoplasty for Treatment of Osteoporotic Vertebral Fractures

| Study | Baseline Mean±SD | 3 days | 2 weeks | 1 month | 3 months | 6 months | 12 months |
|--------------------------------------|--|---|---------|---------|----------|---|-----------|
| Liu et al. 2010 (5) | PV: 7.9±0.7 BK: 8±0.8 Not significant | PV: 2.3±0.5 BK: 2.6±0.6 Not significant | NR | NR | NR | PV: 2.6±0.6 BK: 2.6±0.6 Not significant | NR |
| Wardlaw et al. 2009 (6) (FREE trial) | Pain scores were not reported in the original article. A graph has been provided. Following personal communication with Medtronic Canada, the scores at 1 week, 1 month, 3 months, 6 months, and 12 months were provided for both arms of the study but p-values were not reported (Note: A significant P-value at 12 months was reported in the original article) | | | | | | |

PV, Percutaneous vertebroplasty; BK, balloon kyphoplasty

Table 4. Changes in Physical, Mental, and Social Functioning: Randomized Controlled Trials of Percutaneous Vertebroplasty for Treatment of Osteoporotic Vertebral Fractures

| Study | SF-36 (PCS) Mean difference (95% CI) | RDQ Mean difference (95% CI) | EQ-5D Mean difference (95% CI) |
|--------------------------------------|---|--|---|
| Liu et al. 2010 (5) | NR | NR | NR |
| Wardlaw et al. 2009 (6) (FREE trial) | 1 month: 5.2 (2.9-7.4); P < .0001 3 months: 4 (1.6-6.3); P = .0008 6 months: 3.2 (0.9-5.6); P = .0064 12 months: 1.5 (-0.8 to 3.9); P = .2 | 1 month: 4 (2.6-5.5); P < .0001 12 months: 2.6 (1-4.1); P = .0012 | 1 month: 0.18 ((0.8-0.28); P = .0003 12 months: 0.12 (0.01-0.22); P = .025 |

*in favour of balloon kyphoplasty; CI, Confidence interval

Incidence of New Vertebral Fractures and Adverse Events

In FREE trial, 21 (14%) of patients in kyphoplasty group developed new vertebral fractures; nine (6%) underwent additional kyphoplasty within 6 months of initial treatment. At 12 months, 38 of 115 (33%)

patients in the kyphoplasty group and 24 of 95 (25%) in the non-surgical group has new or worsening radiographic vertebral fractures ($P = .22$). Table 5 shows the incidence of new VCFs and adverse events in the two trials.

Table 5. Incidence of New Vertebral Fractures and Adverse Events: Randomized Controlled Trials of Balloon Kyphoplasty for Treatment of Osteoporotic Vertebral Fractures

| Study | New Vertebral Fracture N (%) | New or Worsening Radiographic Vertebral Fracture N (%) | Adverse Events N |
|-------------------------------|--|---|--|
| Liu et al. 2010 (5) | Within 2 months PV: 0 BK: 2 (4) adjacent | NR | NR |
| Wardlaw et al. 2009 (6) | Within 12 months BK: 21 (14) NSC: NR | BK: 38/115 (33) NSC: 24/95 (25) $P = .2$ | Cardiovascular: <u>Coronary heart disease</u> BK: 7 NSC: 4 <u>Arrhythmia</u> BK: 2 NSC: 2 <u>Pulmonary embolism</u> BK: 3 NSC: 0 <u>Stroke</u> BK: 1 NSC: 1 <u>Hematoma</u> BK: 1 NSC: 0 <u>Other</u> BK: 6 NSC: 0 Respiratory: BK: 11 NSC: 6 Nervous system disorders: BK: 3 NSC: 2 Psychiatric disorders: BK: 3 NSC: 0 Cement extravasation: BK: 48 NSC: N/A Serious adverse events resulted in death: BK: 9 NSC: 7 |

BK, Balloon kyphoplasty; PV, Percutaneous vertebroplasty; NSC, Non-surgical care; NR, Not reported

Quality of the Studies

The Jadad instrument (2) was used to determine the quality of the RCTS on kyphoplasty in terms of how these studies were designed and how they were conducted. The items in this instrument are presented as questions to elicit “Yes” or “No” answers. A numerical score from 0 to 5 is assigned with 0 being the lowest and 5 being the highest quality of the study. (Table 6).

Table 6. Jadad Score Calculation: Randomized Controlled Trials of Percutaneous Vertebroplasty for Treatment of Osteoporotic Vertebral Fractures

| Item | Wardlaw et al. 2009 (6) | Liu et al. 2010 (5) |
|---|--|---|
| Was the study described as randomized (this includes such words as "randomly", "random", and "randomization")? | Yes | Yes |
| Was the method used to generate the sequence of randomization described and was it appropriate (e.g., table of random numbers, computer-generated)? | Yes Computer generated random numbers. Block randomization stratified by sex, etiology, current corticosteroid therapy, any biphosphonate treatment within 12 months. Groups were similar in regards to the age, gender, underlying cause, biphosphonate use, and fracture location. However, Groups were different in regard to the multiple fractures. | Yes Randomization was done by independent central operator. The baseline characteristics of the patients in the two arms were the same. |
| Was the study described as double-blind? | No | No |
| Was the method of double-blinding described and was it appropriate (e.g., identical placebo, active placebo, dummy)? | No | No |
| Was there a description of withdrawals and dropouts? | Yes Consort chart for the study was published. | Yes Consort chart for the study was published. |
| Deduct 1 point if the method used to generate the sequence of randomization was described but was inappropriate (e.g., patients were allocated alternately or according to date of birth or hospital number). | N/A | N/A |
| Deduct 1 point if the study was described as double-blind but the method of blinding was inappropriate (e.g., comparison of tablet vs. injection with no double dummy). | N/A | N/A |

The numerical values for the two RCTs were 3/5 and these two studies were considered as “moderate quality”.

Quality of Body of Evidence

The quality of the body of evidence according to the GRADE system is shown in Appendix 2.

Summary & Conclusions

- No RCT compared kyphoplasty with a sham procedure (similar to the double blinded RCTs on vertebroplasty to control for the placebo effect.
- In the light of vertebroplasty RCTs, no conclusion can be made regarding the difference in pain scores between balloon kyphoplasty and conservative treatment.
- One RCT with moderate quality (Liu et al. 2010) showed no difference in pain scores between kyphoplasty and vertebroplasty.
- In FREE trial the difference in pain scores between the kyphoplasty group and non-surgical care group was statistically significant and clinically important at 1 week after treatment in favour of kyphoplasty. This difference diminished over time; at 12 months follow-up, it was statistically significant but not clinically important.
- In FREE trial significant between group differences in scores for SF-36 PCS (at 1, 3, 6, and 12 months) and RDQ, and EQ-5D (at 1 month and 12 months) was reported.

Glossary

| | |
|--|--|
| Minimal clinically important difference | Minimal clinically important difference reflects the smallest difference in score which is clinically meaningful and important enough to change patient management. |
| Open trial | A randomized trial in which no one is blinded to group assignment |
| Placebo | A placebo is an inactive and generally harmless substance or a procedure without specific influence on the condition being treated. A placebo is given to the patient in place of a real medication. Although it is an inert substance or inactive procedure and has no physiological effect on the patient's specific condition, it may have a psychological effect that arises from patient's expectations concerning receiving the treatment rather than from the treatment itself. Placebos are used in controlled experiments to test the efficacy of another substance |
| Placebo effect | The therapeutic effect produced by placebo |
| Sham | Simulated medical intervention, a placebo |

Glossary for Scales used in RCTs on Balloon Kyphoplasty

Pain score measured on a scale from 0 to 10 with 0 indicating no pain and 10 indicating maximum imaginable pain. The minimal clinically important difference (MCID) in scores in population with back pain is 1.5. (8)

Roland-Morris Disability Questionnaire (RDQ) is a self-administered disability measure on a scale of 0 to 23, with higher scores indicating greater disability and 2-3 points representing the minimal clinically important difference. (9)

European Quality of Life-5 Dimensions (ED-5Q) is an instrument that measures health outcome and consists of 5 dimensions: Mobility, self care, usual activities, pain, and psychological distress; scores range from 0 to 1, with 1 indicating perfect health and 0.074 representing the minimal clinically important difference. (10)

SF-36 is a generic 36-item questionnaire compiled from the Rand Health Insurance Long Form Health Status Scale. The survey consists of 36 questions covering 8 dimensions: Physical function, social function, role physical, role emotional, mental health, vitality, bodily pain, and general health. Each dimension is scored on a weighted 0-100 scale and the overall score is calculated. MCID for SF-36 (PCS) in patients who underwent lumbar spine surgery was 4.9. (11)

Appendices

Appendix 1: Literature Search Strategies

Search date: August 9, 2010

Databases searched: OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, OVID EMBASE, Wiley Cochrane, Centre for Reviews and Dissemination/International Agency for Health Technology Assessment

Database: Ovid MEDLINE(R) <1996 to July Week 4 2010>

Search Strategy:

-
- 1 exp Balloon Dilatation/ or exp Vertebroplasty/ (35665)
 - 2 (kyphoplasty or vertebroplasty).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] (1552)
 - 3 1 or 2 (36642)
 - 4 exp Spinal Fractures/ (6142)
 - 5 exp Fractures, Compression/ (562)
 - 6 ((spinal or spine or vertebr* or compression) adj2 fracture*).ti,ab. (5622)
 - 7 exp Osteoporosis/ (23641)
 - 8 osteoporo*.ti,ab. (26669)
 - 9 or/4-8 (37889)
 - 10 3 and 9 (1217)
 - 11 limit 10 to (english language and humans and yr="2005 -Current") (709)
 - 12 limit 11 to (controlled clinical trial or meta analysis or randomized controlled trial) (29)
 - 13 exp Technology Assessment, Biomedical/ or exp Evidence-based Medicine/ (42417)
 - 14 (health technology adj2 assess\$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] (901)
 - 15 (meta analy\$ or metaanaly\$ or pooled analysis or (systematic\$ adj2 review\$)).mp. or (published studies or published literature or medline or embase or data synthesis or data extraction or cochrane).ab. (84725)
 - 16 exp Random Allocation/ or random\$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] (450663)
 - 17 exp Double-Blind Method/ (61218)
 - 18 exp Control Groups/ (916)
 - 19 exp Placebos/ (10880)
 - 20 (RCT or placebo? or sham?).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] (111574)
 - 21 or/12-20 (581211)
 - 22 11 and 21 (97)

Database: EMBASE <1980 to 2010 Week 31>

Search Strategy:

-
- 1 exp kyphoplasty/ or exp percutaneous vertebroplasty/ (2098)
 - 2 exp balloon dilatation/ (8973)
 - 3 (kyphoplasty or vertebroplasty).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer] (2522)
 - 4 1 or 2 or 3 (11481)
 - 5 vertebra fracture/ or exp spine fracture/ (14431)
 - 6 ((spinal or spine or vertebr* or compression) adj2 fracture*).ti,ab. (10243)
 - 7 exp OSTEOPOROSIS/ (63495)
 - 8 osteopor*.ti,ab. (48519)
 - 9 or/5-8 (84612)
 - 10 4 and 9 (1850)
 - 11 limit 10 to (human and english language and yr="2005 -Current") (1023)
 - 12 Randomized Controlled Trial/ (266254)
 - 13 exp Randomization/ (51020)
 - 14 exp RANDOM SAMPLE/ (2352)
 - 15 exp Biomedical Technology Assessment/ or exp Evidence Based Medicine/ (443856)
 - 16 (health technology adj2 assess\$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer] (1270)
 - 17 (meta analy\$ or metaanaly\$ or pooled analysis or (systematic\$ adj2 review\$) or published studies or published literature or medline or embase or data synthesis or data extraction or cochrane).ti,ab. (110076)
 - 18 Double Blind Procedure/ (94970)
 - 19 exp Triple Blind Procedure/ (15)
 - 20 exp Control Group/ (14259)
 - 21 exp PLACEBO/ or placebo\$.mp. or sham\$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer] (286219)
 - 22 (random\$ or RCT).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer] (668299)
 - 23 (control\$ adj2 clinical trial\$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer] (400267)
 - 24 or/12-23 (1166966)
 - 25 11 and 24 (179)

Appendix 2: GRADE of Evidence

GRADE Table for Randomized Controlled Trials of Percutaneous Vertebroplasty for Treatment of Osteoporotic Vertebral Fractures

| <i>Population</i> | <i>Outcome</i> | <i>Number of studies</i> | <i>Study Design</i> | <i>Quality of Studies</i> | <i>Consistency</i> | <i>Directness</i> | <i>Other Modifying Factors</i> | <i>Grade</i> |
|--------------------------------|----------------------|---------------------------|---------------------|---------------------------|--------------------|-------------------|--------------------------------|-----------------|
| Patients with osteoporotic VCF | Back pain due to VCF | 1 •Liu et al. 2010 | RCT=High | Moderate | No change | No change | N/A | Moderate |
| Patients with osteoporotic VCF | Back pain due to VCF | 1 •Wardlaw et al. 2009 | RCT=High | Moderate | No change | No change | N/A | Moderate |

References

- (1) Medical Advisory Secretariat. Balloon kyphoplasty: an evidence-based analysis. Ont Health Technol Assess Ser [Internet]. 2004 Dec; 4(12) 1-45. Available from: http://www.health.gov.on.ca/english/providers/program/mas/tech/reviews/pdf/rev_kypho_120104.pdf.
- (2) Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996; 17(1):1-12.
- (3) Singh JA, Murphy S, Bhandari M. Assessment of the methodologic quality of medical and surgical clinical trials in patients with arthroplasty. *J Rheumatol* 2009; 36(12):2642-54.
- (4) Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S et al. Grading quality of evidence and strength of recommendations. *BMJ* 2004; 328(7454):1490.
- (5) Liu JT, Liao WJ, Tan WC, Lee JK, Liu CH, Chen YH et al. Balloon kyphoplasty versus vertebroplasty for treatment of osteoporotic vertebral compression fracture: a prospective, comparative, and randomized clinical study. *Osteoporos Int* 2010; 21(2):359-64.
- (6) Wardlaw D, Cummings SR, Van MJ, Bastian L, Tillman JB, Ranstam J et al. Efficacy and safety of balloon kyphoplasty compared with non-surgical care for vertebral compression fracture (FREE): a randomised controlled trial. *Lancet* 2009; 373(9668):1016-24.
- (7) Goodman C. Literature searching and evidence interpretation for assessing health care practices. Stockholm, Sweden: The Swedish Council on Technology Assessment in Health Care. 1993 81 p. SBU-Report No 119E.
- (8) Ostelo RW, Deyo RA, Stratford P, Waddell G, Croft P, Von KM et al. Interpreting change scores for pain and functional status in low back pain: towards international consensus regarding minimal important change. *Spine* 2008; 33(1):90-4.
- (9) Trout AT, Kallmes DF, Gray LA, Goodnature BA, Everson SL, Comstock BA et al. Evaluation of vertebroplasty with a validated outcome measure: the Roland-Morris Disability Questionnaire. *AJNR Am J Neuroradiol* 2005; 26(10):2652-7.
- (10) Walters SJ, Brazier JE. Comparison of the minimally important difference for two health state utility measures: EQ-5D and SF-6D. *Qual Life Res* 2005; 14(6):1523-32.
- (11) Copay AG, Glassman SD, Subach BR, Berven S, Schuler TC, Carreon LY. Minimum clinically important difference in lumbar spine surgery patients: a choice of methods using the Oswestry Disability Index, Medical Outcomes Study questionnaire Short Form 36, and pain scales. *Spine J* 2008; 8(6):968-74.