MTAC REPORT

Topic:	**Kyphoplasty (balloon kyphoplasty, BKP) for the treatment of vertebral compression fractures.**
Date requested:	**4/21/2008**
Date reviewed:	**8/4/2008**
Previous reviews:	**2/5/2001, 6/9/2004, and 6/6/2005**
Requested by:	**Candace Carroll, RN**

Background/Description:

Vertebral compression fracture (VCF) is becoming an important health issue especially in Western societies due to the aging population osteoporosis and associated fractures. It is estimated that about five million new vertebral fractures occur worldwide each year. In the US, osteoporosis is responsible for more than 1.5 million fractures annually, half of which are vertebral. Other causes of VCFs include multiple myeloma, metastatic cancers, hemangiomas, and traumatic compressions.

Vertebral compression fractures may be asymptomatic, but are more frequently associated with radicular pain, motor and/or sensory deficits, spinal cord compression, and kyphosis. These may impair the patient's quality of life, and lead to higher risk of morbidity and mortality (Atalay 2005, Barragan-Campos 2006, Tylor 2007).

Conservative management of VCFs includes external bracing, analgesics, and bed rest. Some patients may require constant use of narcotic medication and prolonged bed rest to control the pain. The extended duration of inactivity may aggravate the loss of bone density, muscle mass, and muscle strength which may potentially cause additional fractures.

Over the last twenty years, two minimally invasive techniques to augment the vertebral bodies and reduce pain have been developed for the treatment of osteoporotic VCFs. The first percutaneous vertebroplasty (PV) was performed in France, in 1984 by Deramond and colleagues for the treatment of painful vertebral angioma. Its use was then expanded to vertebral fractures caused by osteoporosis, trauma, tumors, or vertebral osteonecorsis. Currently PV is most frequently used to treat patients with painful osteoporotic VCFs. The procedure involves the percutaneous injection of bone cement (generally PMMA) into the fractured vertebral body under fluoroscopic guidance. Vertebroplasty however, does not address spinal malalignement, and is associated with a high rate of cement leakage (Berlamann 2004).

Kyphoplasty, also known as balloon kyphoplasty (BKP), was introduced in the late 1990s as a modification of vertebroplasty to address both the pain as well as the kyphotic deformity usually associated with the fracture. The procedure involves the percutaneous placement of inflatable bone balloon called tamps into the vertebral body, under fluoroscopic control, to restore height and reduce kyphotic deformity before stabilization with PMMA. Inflation of the tamps with radio-opaque contrast media lifts the endplates

and restores the vertebral body height. The tamps are then removed creating a cavity which is then filled with viscous polymethylmethacrylate (PMMA). It is believed that the cavity formation and the use of more viscous cement introduced with less pressure, compared to vertebroplasty leads to lower risk of cement extravasation (Atalay 2005, Tylor 2007).

Kyphoplasty however, may still be associated with serious complications e.g. extravasation of PMMA into the spinal canal, neural foramina, and paraspinous veins leading to serious neurological and cardiopulmonary complications.

Kyphoplasty was FDA approved in 1998, based on its equivalence to devices already marketed. The technology was reviewed by MTAC in 2001, 2004, and 2005 and did not meet the Group Health medical Technology Assessment criteria. At that time, the published literature consisted of small case series which did not provide sufficient evidence to determine the efficacy and safety of kyphoplasty in the management of vertebral compression fractures.

Assessment objective:

To determine whether kyphoplasty leads to better outcomes than vertebroplasty or other non-operative treatments used in the management of vertebral compression fractures due to osteoporosis, trauma, multiple myelomas, or metastatic cancer.

Literature search:

1) The Medline database was searched from 2005 through June 2008 using the terms *balloon kyphoplasty, percutaneous, bone cementoplasty, vertebral compression fractures,* and *osteoporosis*", with variations.
2) The search was limited to English language publications and human populations.

Screening of articles:

The search yielded over 90 articles on balloon kyphoplasty. Many were reviews and technical reports. No randomized controlled trials that compared the procedure with vertebroplasty or conservative therapy were identified. There were four meta-analyses of non-randomized controlled studies and case series. All four included almost the same studies, and two were performed by the same group of authors. The search also revealed two non- randomized comparative studies published after the meta-analyses. One (N=21) compared kyphoplasty to vertebroplasty for the treatment of painful osteoporotic or traumatic VCFs, and the other (N=60) compared kyphoplasty with standard medical treatment of osteoporotic or traumatic VCF. The studies on the use of kyphoplasty for severe back pain due to metastatic disease were small case series with no control or comparison groups. The most recent meta-analysis and the two comparative studies were critically appraised.

Taylor RS, Fritzell P, Taylor RJ. Balloon kyphoplasty in the management of vertebral compression fractures: an updated systematic review and meta-analysis. *Eur Spine J* 2007;16:1085-1100.

De Negri P, Tirri T, paternoster G, et al. Treatment of painful osteoporotic or traumatic vertebral compression fractures by percutaneous vertebral augmentation procedures. *Clin J Pain.* 2007;5:425-430.

Grafe IA, Fonseca KD, Hillmeier J, et al. Reduction of pain and fracture incidence after kyphoplasty: 1-year outcomes of a prospective controlled trial of patients with osteoporosis. *Osteoporos Int* 2005;16:2005-2012.

Reviewer's summary (Nadia Salama, MD, PhD):

The body of evidence on the safety and efficacy of balloon kyphoplasty (BKP) in the treatment of vertebral compression fractures consisted of multiple case series and few non-randomized studies that compared BKP to either vertebroplasty or the standard conservative therapy. Several authors pooled the results of these comparative and non-comparative series in a number of meta-analyses. However, the quality of meta-analyses and the strength of their conclusions depend on the quality of the included studies. The studies included in the published meta-analyses for BKP were too small, and had their methodological flaws and potential selection and observation bias. The comparative studies were non-randomized and the authors did not discuss how and why patients were selected for each of the procedures. There was evidence of publication bias as well as significant heterogeneity between the studies included in the meta-analyses. The studies differed their inclusion/exclusion criteria, outcome measures, scales used, and scoring systems, as well as duration and completeness of follow-up. Moreover the results were unblinded and many of the outcomes were subjective.

The comparative studies published after the meta-analyses were also too small, non-randomized, unblinded, with relatively short follow-up duration, as well as other validity threats and do not allow making conclusions as regard the efficacy and safety of the procedure.

In conclusion, the published literature does not provide sufficient evidence to determine the benefit of the procedure in relieving pain, improving function, and reducing rate of vertebral fractures. There is also insufficient evidence to determine its long lasting effect on pain relief or its adverse effects on the spine. Large well conducted randomized controlled trials, with long term follow-up duration are needed to objectively compare balloon kyphoplasty to conventional treatment and other percutaneous techniques, and to determine its long-term safety and efficacy in improving function and reducing pain, disability, and complications associated with vertebral compression fractures.

Additional references:

Atalay B, Caner H,Gokce C, et al. Kyphoplasty: 2 years of experience in a neurosurgery department. *Surg Neurol* 2005;64:S2;76-S2:76.

Barragan –Campos HM, Vallee J-N, Lo D, et al. Percutaneous vertebroplasty for spinal metastases: Complications. *Radiology* ;238:354-362.

Berlamann U, Franz T, Orler, et al. Kyphoplasty for treatment of osteoporotic vertebral fractures: a prospective non-randomized study. *Eur Spine J*. 2004;13:496-501.

Evidence Table

Clinical Area: **Kyphoplasty for the treatment of osteoporotic compression fractures.**

Reference: **Taylor RS, Fritzell P, Taylor RJ. Balloon kyphoplasty in the management of vertebral compression fractures: an updated systematic review and meta-analysis. *Eur Spine J* 2007;16:1085-1100.**

Study Type: Meta-analysis of nonrandomized studies and case series.

Study Aim: To determine the efficacy and safety of balloon kyphoplasty (BKP) in the management of vertebral compression fractures.

Outcomes

Primary: Reduction in pain, increase in vertebral height, and improvement in functional capacity.

Design

- *Focused on a discrete clinical question:* Yes.
- *Explicit description of literature search:* Yes.
- *State inclusion and exclusion criteria for studies:* Inclusion: 1. Randomized and non-randomized trials, observational studies and case series, 2. Patients with VCFs of osteoporotic or neoplastic etiology, 3. Kyphoplasty compared with any invasive, semi-invasive or medical therapy, and 4. Reported at least one of the following outcomes; efficacy, pain relief, functional capacity, health related QOL, deformity correction, safety, cement leakage, incident fractures or other complications. Exclusion: Studies reporting on burst fractures and fractures due to trauma, including kyphoplasty combined with other invasive or semi-invasive therapy, patients receiving repeat interventions, case reports, or studies published only in the abstract form..
- *Description of study populations:* Yes.
- *State criteria used to evaluate quality of studies*: Yes.
- *Method used to synthesize data (fixed-effects model, random-effects model, both):* Both the random effects and fixed effects models were used.

Validity:

- *Is the study type of the included studies appropriate for the question(s) being asked?* No, the meta-analysis included randomized as well as non randomized comparative studies, observational studies, and case series.
- *Did two or more independent reviewers select studies and extract data?* Yes.
- *Data tested for homogeneity?* Yes.
- *If data were heterogeneous, was the analysis method appropriate? (E.g. stratified analysis or random effects model)?* Yes.
- *Did the authors do sensitivity analysis to examine robustness of findings (e.g. by quality of studies)?* No
  How did the authors address possible publication bias? Publication bias was assessed using funnel plots and the Egger test.

Conclusions regarding validity of methods:

The meta-analysis included comparative non randomized trials, observational studies and case series. The methodology of the meta-analysis was valid, however its quality and strength is dependent on the methodological quality of the studies it includes.

Results:

- The meta-analysis included 8 comparative trials (n=313 patients with 481 fractures), and 21 case series (2,047 patients treated with BKP on 3,301 vertebral levels) published between March 2004 and April 2006.
- Five of the comparative studies compared BKP to vertebroplasty, and three studies compared it with conventional medical care.
- Two of the four comparative studies were judged to have low threat to bias, and 15 of all studies included were assessed to have a high threat to bias.
- Median age 70.1 years, 66% were women, 84% symptomatic VCF, 10% multiple myeloma, 5% metastatic lesions, and 1% hemangioma.
- Patients were generally refractory to medical treatment.
- Duration of follow-up ranged from immediate post-procedure to 3 years.
- There was significant heterogeneity between studies in pain relief and cement leakage.
- There was evidence of publication bias.

Outcomes with BKP versus conventional medical care in the comparative studies

Outcomes	No of studies	Effect size (mean difference) (95% CI)	P value
Pre-post pain (VAS mm)			
3 months	1	-4.5 (-6.1 to -2.9)	<0.0001
6 months	2	-1.6 (-2.0 to -1.2)	<0.0001
12 months	1	-1.7 (-2.1 to -0.3)	<0.0001
36 months	1	-1.6	<0.0001
Pain-related office visits			
6 months	1	-5.3 (-9.7 to -0.18)	0.019
12 months	1	-6.3 (-11.8 to -0.8)	0.025
Pre-post functional capacity			
6 months (disability index)	2	-1.2 (-1.7 to -0.8)	<0.0001
12 months (disability index)	1	-6.2 (-27.8 to 15.7)	<0.574
Pre-post vertebral height			
6 months	1	10.3 (2.3 to18.3)	0.012
12 months	1	12.6 (4.8 to 20.4)	0.002
Pre-post kyphotic angle (^{O})			
6 months	1	-5.3 (-9.3 to -1.3)	0.009
Days in hospital	1	-10 (-16.7 to -3.3)	0.003

There was no significant difference in the use of opiate medication at 6 months (reported in one study)

Kyphoplasty versus vertebroplasty

- The outcome data presented were mainly obtained from single studies.
- Data were pooled from 2 studies only for two outcomes (pre-post pain, and functional capacity at 12 months).
- There were no significant differences between the two interventions in the pre-post pain and functional capacity.
- A significant difference was observed (in one study) between BKP and vertebroplasty in the pre-post vertebral height only postoperatively (mean difference 5.8mm), but not at 6 or 12 months after the procedure.
- There was a significant difference between BKP and vertebroplasty in the pre-post kyphotic angle postoperatively (one study) which was sustained at six months and at 12 months with mean differences of -6%, -5% and -6% respectively.

Meta-analysis of case series (Post vs. pre BKP)

Outcomes	No of studies	Pooled mean reduction /improvement (95% CI)	p value
Pain reduction	4	5.4 mm (-6.4 to -4.4)	<0.0001
Functional capacity	4	1.1(0.6-1.5)	<0.0001
Vertebral height	9	21% original height (15-26)	<0.0001
Kyphotic angle	12	-6.3^{o} (-5.8 to -6.7)	<0.0001
QOL*(SF 36 [0-100])			

* Significantly improved in 6 of the 8 domains.

Adverse events

Events	No of events*	Probability (95% CI)	Rate events /1000 patient or fracture years
Cement leakage	193/2239	9.0% (7.4-11.2)	81
New vertebral fractures			
Overall	172/1151	13.6% (9.0-20.7)	111
Adjacent	110/871	13.8% (11.0-17.4)	94
Pulmonary embolism	1/377	0.10% (0-1.7)	1.7
Spinal cord compression	1/431	0.2% (0-0.8)	1.6
Nerve root pain	2/173	0.40% (0-1.2)	1.7
Mortality	35/552	3.2% (0.7-5.6)	44

* Per vertebrae cement leakage and for nerve root pain.

Authors' Conclusions:

The authors concluded that prospective studies with at least 12 months of follow-up show that balloon kyphoplasty are more effective that medical management and as least as

effective as vertebroplasty in the management of osteoporotic vertebral compression fractures**.**

Reviewer's Conclusions:

The meta-analysis methodology was valid however it did not include any RCTs, just mainly case series, and few small non-randomized controlled studies. Two of the comparative studies and three fourths of the case series were judged by the authors of the meta-analysis to be of low methodological quality. There was also evidence of publication bias, and heterogeneity between the studies. Pooling the results in meta-analysis could not be performed for the majority of outcomes due to the lack of reported data. The authors based their conclusion on the results of very few small non-randomized controlled with limitations, and that could not be pooled in a meta-analysis due to the limited data provided.

Evidence Table
Non-randomized trials comparing kyphoplasty with vertebroplasty or conservative standard therapy
For the management of vertebral compression fractures

Study	***Study type, aim, participants, methodology***	***Results***	***Validity***
De Negri 2007	Study type: Nonrandomized comparative study . Aim: To determine and compare the safety and efficacy of kyphoplasty (BKP) and vertebroplasty (PV) in the management of pain and mobility among patients with vertebral fractures due to osteoporosis or trauma. Participants: N=21men and women. Inclusion /exclusion criteria: ≥1 vertebral fracture lasting <6 months, with integral posterior body and not responding to chronic pain medication. Those in poor clinical conditions or with vertebra plana, or structural alteration of posterior vertebral body were excluded. Intervention: After clinical exam, spinal radiography and MRI, the patients underwent either PV or BKP without randomization. Patients with a severe vertebral collapse were treated with VP. Outcomes: 1. Reduction in pain as measured by a Visual analog Scale (VAS) before the procedure, one hour after the procedure, 48 hours, I month, 3 months and 6 months later. 2. Functional improvement measured by the Oswestry disability Index (ODI) before the procedure and after 6 months. 3. Cement leakage and general complications.	11 KPs at 15 vertebral levels (11 thoracic and 4 lumbar) and 10 PVs at 18 vertebral levels (6 thoracic and 10 lumbar) were performed. **Outcomes** Pre-treatment Post-treatment p value ***Pain (VAS)*** PV 8.36 ± 1.21 0.55± 0.52 <0.05 BKP 8.30 ± 1.25 0.70± 0.67 <0.05 P value NS NS ***Functional disability (ODI)*** PV 37.36 ± 5.16* 12.55± 1.63† <0.05 BKP 38.40 ± 4.38** 12.10± 1.60†† <0.05 P value NS NS *74% disability, ** 77% disability, †24% disability, ††23% disability ***Complications*** Cement leakage % PV 37.6 BKP 0.0	This was a small non-randomized, unblinded single center study, with potential bias and insufficient power to detect significant difference between the two interventions. The authors did not discuss the patients' characteristics, and how they were selected for each procedure, except for two with a vertebral collapse too severe to permit the insertion of a balloon. The study did not address the effect of the procedures on the restoration of vertebral heights. .

Study	*Study type, aim, participants, methodology*	*Results*	*Validity*
Grafe 2005	Study type: Nonrandomized comparative study. (Long term follow-up of an earlier study). Aim: To evaluate the persistence of clinical benefits of balloon kyphoplasty on pain reduction, and assess the incidence of vertebral fracture due to the procedure among patients with primary osteoporosis. Participants: N=60, mean age 69 years, 81.65% women, and 73% with >3 fractures. Inclusion /exclusion criteria: Chronic back pain not relieved by analgesics, due to an osteoporotic vertebral fracture older than 12 months. Patients with severe degenerative spine alterations, nerve compression by disc prolapse, vertebra plana, fractured posterior wall, poor clinical conditions, were excluded. Intervention: After undergoing a clinical exam, spinal radiography, CT and MRI, the patients eligible for kyphoplasty were offered to receive the procedure or intensified conservative treatment including optimized pain medication and physical training as an alternative. Outcomes: 1. Radiomorphometric measurements of vertebral body height. 2. Reduction in back pain as measured by a Visual analog Scale (VAS) and improvement in mobility (EVOS questionnaire) 3. Health care utilization. 4. Incidence of new vertebral fractures, 5. Cement leakage and other adverse events.	40 patients underwent 73 procedures of BKP, and 20 chose the conservative therapy the day before planned the kyphoplasty and were used as a control group. **Outcomes** ***Radiomorphometric outcomes (midline vertebral body height)*** Kyphoplasty Postoperatively vs. baseline p<0.0001 6 and 12 months vs. baseline p<0.0001 Conservative therapy Post operative vs. baseline progressive height loss p<0.001 Kyphoplasty vs. conservative therapy p<.0001 ***New vertebral fractures after 12 months*** n/N % Kyphoplasty 7/40 17.5 Conservative 11/20 55.0 P value 0.008 New fractures in adjacent vertebrae 6 /84 in kyphoplasty, vs. 4/41 in conservative therapy, p=0.728 ***Pain (VAS)*** Kyphoplasty Postoperatively vs. baseline p<0.0002, 6 and 12 months vs. baseline p<0.0001 Conservative therapy Post operative vs. baseline NS Kyphoplasty vs. conservative therapy p<.0.019, and 0.008 at 6 and 12 months respectively	This was a relatively small non-randomized, unblinded single-center study, with potential selection and observation. The controls were patients who refused to undergo kyphoplasty the day before it was planned. .

		(At 12 months 77.5% of the patients in the kyphoplasty group showed improvement in the VAS score vs. 55% of the controls). ***Mobility (EVOS) score)*** Kyphoplasty Postoperatively vs. baseline ($p<0.003$), 6 and 12 months vs. baseline $p<0.0001$, and $=0.0003$ respectively. Conservative therapy Post operative vs. baseline NS Kyphoplasty vs. conservative therapy At 6 months $p=0.027$ At 12 months $p=0.105$ After 12 months 75% of the patients in the kyphoplasty group showed improvement in the EVOS score vs. 55% of the controls ($p=0.144$). ***Pain-related doctor visits in 12 months*** 5.3± 0.7 in the kyphoplasty group vs. 11.6± 2.7 in the controls ($p=0.006$) ***Complications*** Cement leakage occurred in 12 vertebrae per 72 kyphoplasty procedures (16%) (5 ventral, 7 lateral and no posterior)	