PAIN MANAGEMENT BY WHO STEP LADDER PATTERN PROTOCOL IN CASES OF CERVICAL CANCER

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ABSTRACT

To assess pain in cases of cancer cervix and to evaluate the response to pain management according to WHO step ladder pattern in cases of cancer cervix, total 209 carcinoma cervix diagnosed and admitted case were recruited in the study. Baseline pain score was measured for each patient. For mild to moderate pain (VAS ≤ 7) , step 1 analgesic, NSAID, diclofenac sodium (50 mg TDS) was prescribed. Pain scores were reevaluated after 48 hrs and change of score was recorded. If pain persisted (same score), worsened (score increased) or score decreased but with a VAS score of > 4 , case was considered as non responder and patient was switched to step 2 analgesic. Step 2 was also applied directly to patients presenting with severe pain (VAS >7) at the time of recruitment. Drugs used in step 2 was oral tramadol (50 mg QID) along with Diclofenac (50 mg TDS) . VAS Score was reevaluated after 48 hrs. If score still remained above 4; adjuvant analgesics (Amitryptiline 25-75 mg OD, Prednisolone 5mg BD – 10 mg/day) were added to step 2. Step 2 non responders were treated with step3 protocol. In step 3, tab morphine (10 mg BD upto maximum 30 mg BD) was given after stopping all other drugs . After 48 hrs, scores were re evaluated; if scores remained >4; adjuvant analgesics (Amitryptiline 25-75 mg OD, Prednisolone 5mg BD – 10 mg/day) were added. After 48 hrs if still pain scores did not decrease to <4, case was declared as failure . The WHO algorithm was followed as per the response of the patients. Outcome showed decrease in pain score using Visual Analogue Scale Score. 209 patients were enrolled in the study. 60 patients had no pain at baseline. Out of 149 patients with pain, 44.9 % (67) patients achieved complete pain relief at step 1. Out of the remaining 82 patients , 5 were lost to follow up. 49.3 % (38) achieved complete relief at step 2 . Only 39 patients did not reach score of zero after step 2 but 35 (89.7%) out of them achieved complete relief after step 3. Out of 142 patients (excluding lost to follow up), 2 cases were declared as failure. Among these failure cases, one of them had metastasis of femur and symphysis pubis; bisphosphonates were started. Other patients had bladder and bowel involvement diagnosed on repeat cystoscopy. This WHO guideline implementation study supports use of algorithm in decision making for cancer pain management. Following the same we were able to achieve effective pain relief in 96% of our patients with failure rate of only 4%. It further helped to reduce patient's agony and improved the quality of life.

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INTRODUCTION

Pain is a subjective multidimensional experience unique to an individual, with a potential impact on function, status and quality of life. Yet it is one of the most common unattended and unsolved problem for cancer patients. Cancer cervix is one of the leading cause of cancer death among women worldwide. Incidence of new cancer patients in India is about 100,000 per year and 70% or more of these are stage 3 or higher at the time of diagnosis (Venugopal T C 1995). Pain is a debilitating symptom associated with cancer cervix. It occurs in 25-50% patients with newly diagnosed malignancy, in more than 75% of those with advanced disease, and in 33% of those undergoing treatment (Van den Beuken 2007) . Pain in patients with cancer cervix is a complex process that occurs from many causes like somatic, visceral, neuropathic and bone pain (Ashby 1992) . Ninety percent of pain in cancer cervix is a complex resulting from the tumor itself, in which 70% of pain develops from tumor invading or compressing uterosacral ligament and sacral plexus, and 20% of cancer pain is related with its treatment (radiation and chemotherapy related neurotoxicity). Rest 10% of pain is due to unrelated illness. Common sites of pain in cancer cervix are back, lower abdomen, flank, buttocks and perineum. Pain can be pressure like, dull aching , burning , cramping or lancinating (Saphner 1989).

WHO recommended a stepladder pattern algorithm as a guideline for pharmacological management of cancer pain in 1986 (WHO 1996) which was updated in 1996. It describes

three step progression from the use of nonopoid medication (acetaminophen, dipyrone, NSAIDs) to weaker opoids (codeine, dextropropoxyphene , tramadol) and then strong opioids (morphine, methadone, oxycodone, hydromorphone, buprenorphine) depending on pain intensity. Using this, pain control can be achieved in 85% of patients. The use of guidelines has been studied in over 30,000 patients, proving its usefulness and efficacy (Zech 1995). However, despite the availability of effective guidelines for pain control, most cancer patients have a poor quality of life which increases their agony. Effective pain management improves quality of life as well as the ability to tolerate diagnostic and therapeutic procedures (Blanchard 1986). Henceforth, this study was done to assess the need of pain management in cancer cervix and to evaluate the efficacy of pain management by WHO stepladder pattern in the patients of cancer cervix.

MATERIALS AND METHODS

This pilot prospective cohort study was conducted in the Department of Obstetrics and Gynaecology, in collaboration with Department of Anaesthesia, KGMU , over a period of one year. Total 209 patients were diagnosed as carcinoma cervix, admitted in the Department of Obstetrics and Gynaecology were recruited in the study. These patients were either receiving or were planned for chemoradiation. Patients with systemic debilitating diseases (renal failure, Diabetes Mellitus, HIV, respiratory and hepatobilliary diseases), peptic ulcer, bleeding diathesis , thrombocytopenia, epilepsy or history of seizures and patients who underwent major surgery within 2 weeks were excluded. Written informed consent was taken from each patient before pain assessment and management. Demographic details and complete history was recorded. General, systemic and gynaecological examination was done. Variables recorded were age, parity, presenting complaints, stage of disease, delay in start of treatment, uterosacral ligament involvement, radiotherapy, anaemia, smoking/ tobacco, poor family support.

PAIN ASSESSMENT

Initial pain assessment was done by taking detailed pain history regarding pain characteristics like intensity, location, quality, duration and temporal pattern. Pain intensity was measured by visual analogue scale.VAS is a graduated line 100 mm in length , anchored by word descriptors at each end like no pain and worst pain. The patient marks on the line the point that they feel, represents their perception of their current state. The VAS score is determined by measuring in millimeters from the left end of the line to the point that the patient marks. According to VAS score pain was categorized into mild, moderate and severe categories. Patients with mild pain, have VAS score in the range of 1-4, those having moderate pain have VAS score, in the range of 5-6 and patients having severe pain have VAS score ≥ 7. Subsequent assessment was done after giving the drug , at regular intervals and at each new report of pain. It was done 24-48 hours after oral administration.

PAIN MANAGEMENT

Oral route was preferred with a fixed schedule dosing to manage constant pain and prevent pain from worsening. Rescue (breakthrough) dose was combined with regular fixed schedule analgesics to control episodic exacerbation. Baseline pain scores were measured for each patient. For mild to moderate pain (VAS ≤ 7) , step 1 analgesic, NSAID, diclofenac sodium (50 mg TDS) was prescribed. Pain scores were reevaluated after 48 hrs and change of score was recorded. If pain persisted (same score), worsened (score increased) or score decreased but with a VAS score of > 4 , case was considered as non - responder and patient was switched to step 2 analgesic. Step 2 was also applied directly to patients presenting with severe pain (VAS >7) at time of recruitment. Drugs used in step 2 was oral Tramadol (50 mg QID) along with Diclofenac (50 mg TDS) . VAS Score was reevaluated after 48 hrs**.** If score still remained above 4; adjuvant analgesics (Amitryptiline 25-75mg OD, Prednisolone 5mg BD – 10 mg/day) were added to step 2. Step 2 non - responders were treated with step3 protocol. In step 3, tab Morphine (10 mg BD upto maximum 30 mg BD) was given after stopping all other drugs. After 48 hrs, scores were reevaluated; if scores remained >4; adjuvant analgesics (Amitryptiline 25-75 mg OD, Prednisolone 5mg BD – 10 mg/day) were added. After 48 hrs if still pain scores did not decrease to <4, case was declared as failure as per study protocol and some other palliative measures (neurolytic sympathetic plexus block, epidural block, epidural neurolysis) was applied to relieve pain. Once the patient's pain score declined to 0; she was followed up to 2 weeks so as to check any increase in pain. At each step of the ladder, adjuvant drugs (laxatives/stool softeners ,antiemetic) were considered in selected patients to treat concurrent symptoms (Mercadante 2001).

STATISTICAL TOOLS

Was done using SPSS (Statistical Package for Social Sciences) version 15.0 statistical analysis software

RESULTS

A total 209 patients of carcinoma cervix were enrolled in the study. The mean age of patients in this study was 49.7 yrs and maximum patients were in the age group 41-50 years (48%). Majority of the subjects were multiparous (67.5%), residing in rural areas (80.3%), of low socioeconomic status (80%) and illiterate (85%) . Most common presenting symptoms were discharge per vaginum (75%), pain (61%), postmenopausal bleeding (44%) , post coital bleeding (15.7%), bladder and rectal symptoms (10%). Most common type of pain was low backache (70%) followed by lower abdominal pain (52%) and perineal pain (34.6%). Majority of patients had pressure like continuous aching pain (74%) with the duration of onset of pain being < 6 month in most of the patients. After pain assessment of 209 patients, 149 were found eligible for pain management as per WHO step ladder pattern and their response was analysed Out of 149 patients with pain, 44.9 % (67) patient achieved complete pain relief at step 1. Out of

the remaining 82 patients , 5 were lost to follow up. 49.3 % (38) achieved complete relief at step 2 , however 5 patients also required adjuvant medication along with step 2. Only 39 patients did not reach score of zero after step 2 but 35 (89.7%) out of them achieved complete relief after step 3. Out of 142 patients (excluding lost to follow up), 2 cases were declared as failure. Among these failure cases, one of them had metastasis of femur and symphysis pubis; bisphosphonates were started. Other patient had bladder and bowel involvement diagnosed on repeat cystoscopy.

Association between involvement of uterosacral ligament and step of pain relief was analysed using chi square test. Uterosacral ligament involvement was associated with higher step of pain relief ($p<0.0001$). In 93% of patients with uterosacral involvement, no pain relief was seen at step 1.Other factors like presence of anaemia, addiction, delay in start of treatment, post radiotherapy, poor family support , old age , illiteracy , low socioeconomic status were studied using logistic regression analysis. These factors did show an increased risk ratio but were not statistically significant. Side effects were observed in all analgesic group of patients, more commonly with Morphine (30.2%) and Tramadol

Table 1 : Correlation between stage of the disease and severity of pain

Stage	No.	Pain	No Pain	mild	Moderate	Severe
1	24	7 (29.2%)	17(70.8%)	4	2	1
2	88	57(64.8%)	31(35.2%)	6	42	9
3	90	78(86.7%)	12(13.3%)	8	29	41
4	7	7(100%)	0 (0%)	0	0	7
Total	209	149	60	18	73	58
RESPONDERS				**18**	**72**	**57**
NON RESPONDERS				**0**	**1**	**1**

1. Stage Vs Pain: $\chi^2=35.850$ (df=3); $p<0.001$

Table 2 : Correlation between initial pain scores and response to step ladder therapy

Step	VAS	No.	Responders	Non Responders	Lost to follow up	Response to adjuvants
1	1-6	91	67 (73.6%)	24	-	-
2	>=7	58	17(29.3%)	41	-	-
2	nonresponders of step1	24	16/23 (69.6%)	7/23 (30.4%)	1	
2	direct + nonresponders of step1	81	33/81(40.7%)	48/81 (59.3%)	-	-
2+adjuvants	nonresponders of step 2	48	5	39	4	5/44(11.4%)
3	nonresponders of step 2	39	35 (89.7%)	4 (10.3%)	-	
3+adjuvants	nonresponders of step 3	4	2	2	-	2/4(50%)

Table 3 : Correlation between stage of disease and response to pain , the proportion of responders decreased from stage 1 to stage 4 showing a statistically significant inverse

STAGE	NUMBER	RESPONDERS	NONRESPONDERS (including lost to follow up)
1	7	7 (100%)	0
2	57	57 (100%)	0
3	78	75 (96.1%)	3 (all 3 lost to follow up)
4	7	3 (42.9%)	4 (2 were lost to follow up)

association between stage and response rate ($p< 0.001$)

$\chi^2=54.219$ (df=3); $p<0.001$

Table 4 : Correlation between stage of the disease and step of pain relief

STAGE	STEP 1 (n= 67)	STEP 2 (n = 38)	STEP 3 (n = 37)	FAILED (n= 2)
1 (n= 7)	6/7 (85.7%)	1 /7 (14.3%)	0	0
2 (n=57)	43/57 (75.4%)	14/57 (24.6%)	0	0
3 (n=75)	18/75 (24 %)	23/75 (30.7%)	33/75 (44%)	1/75 (1.3%)
4 (n=5)	–	0/5 (0%)	4/5 (80%)	1/5 (20 %)

Table 5 : Shows an inverse association between response rate and initial pain category (p<0.001)

INITIAL PAIN SCORE	RESPONDERS	NON RESPONDERS
1-4	18	0
5-6	72	1
>=7	52	1 + 5 (lost to follow up)

χ^2=6.824 (df=2); p<0.001

Chi square test 'p' value = 0.0001

(25%) compared from Diclofenac, constipation was more commonly seen with Morphine (25.6%) compared from Tramadol (8.5%). Epigastric pain was observed only in Diclofenac group (10.9%). Physical dependence, tolerance and addiction was not seen.

DISCUSSION

Van den Beuken (2007), in a review showed that prevalence of pain was 50% in all cancer stages, 64% in patients with metastatic or advanced stage disease, 59% in patients on anticancer treatment and 33% in patients after curative treatment. In the present study, 71.3 % patients had pain as the presenting complaint and majority of the patients (57%) with pain were in advanced stage (3 and 4) followed by 38.2 % in stage 2 and 4.6 % in stage 1 of cancer cervix. Thus, incidence of pain increasing with stage of the disease. Pain evaluation in the present study was done using Visual analogue scale (Wewers 1990). Various other methods of pain measurement are Edmonton symptom assessment (Bruera 1991), Wisconsin Brief pain inventory (Cleeland 1994), Memorial pain assessment card (Fishman 1987), McGill pain questionnaire (Melzac 1987), Hopkins pain rating instrument (Grossman 1992), Simple descriptive scale (McGrath 1998), Numeric pain distress scale and Facial scale. The goal of initial assessment of pain is to characterize the pathophysiology of pain and to determine the intensity of pain and patients ability to function.

Ventafridda V etal (1990), in a study found NSAIDs effective and relatively well tolerated in treatment of cancer pain. McNicol E etal (2004) found that nonsteroidal anti-inflammatory drugs were preferred for mild to moderate cancer pain. Pain intensity increases with advancing stage due to involvement of ureters, pelvic wall or sciatic nerve routes. This was confirmed with findings of this study since the severity of pain increased (p<0.001) with stage of disease.

Radbruch L etal (1996) found that Tramadol is safe and effective in the treatment of mild to moderate cancer pain when used in combination with non opoids In present study, Step 1 response rate was 73.6%. However, among patients directly recruited for step 2 the response rate was only 29.3%, showing a statistically significant difference (p<0.001). This indicates that among patients directly recruited for step 2, the protocol does not seem to be a good-fit. Among patients recruited to step 2, after failure of step 1, the response rate was 69.6% which was at par with the response rate at step 1 (73.6%) (p=0.696). This indicates the appropriateness of protocol. Overall response among patients recruited to step 2 (both directly recruited and those promoted to step 2 after failure of step 1) was 40.7% which is significantly lower as compared to that for step 1 (p<0.001). As highlighted above, this difference in response of two steps was owing to low response rate observed amongst directly recruited subjects of Step 2.

Response to step 3 (89.7%) was significantly higher as compared to both steps 1 and 2, thereby indicating its utility as the terminal, final step of the protocol. 40.7 % of severe pain patients responded to Tramadol and 89.7 % of severe pain patients responded to morphine. Thus, Morphine was found to be more effective drug in (p<0.001) for severe pain. Gatti A et al (2009) found that with Morphine therapy 30 -60 mg / day VAS score reduced significantly. They concluded that Morphine therapy could be implemented as a standard therapy to manage moderate to severe chronic pain in cancer patients. Grond S. etal (1999) compared the efficacy and safety of high dose Tramadol and low dose Morphine for mild to moderate cancer pain and observed high dose Tramadol is equally effective and safe for mild to moderate cancer pain as low dose Morphine. Wilder Smith etal (1994) observed that for strong cancer pain Morphine is more effective than Tramadol.

Pain intensity at initial assessment is a significant predictor of response rate in pain management amongst cancer patients. We observed that as the initial VAS score increased, the response rate decreased (p<0.001). Robin et al (2009) in a study found that pain with moderate to severe intensity required significantly higher opioid doses and more adjuvant modalities.

Guay D R (2001) evaluated the analgesic benefits of tricyclic antidepressants in cancer patients. Wooldridge J E etal (2001)

Table 6 : Shows comparison of response at various steps of treatment

Comparison of response to therapy at different steps	P - value
Step 1 vs Direct recruited for Step 2	χ^2=28.287; p<0.001
Step 1 vs Non-respondents of Step 1 given Step 2 therapy	χ^2=0.153; p=0.696
Step 1 vs Overall Subjects of Step 2 therapy	χ^2=19.043; p<0.001
Step 2 vs Adjuvants added to step 2	χ^2=11.630; p<0.001
Step 3 vs Step 1	χ^2=4.196; p=0.041
Step 3 vs Step 2	χ^2=25.743; p<0.001

in a study reported that anti-inflammatory component of corticosteroid plays role to relieve pain in cancer cervix. The response to adjuvants was 11.4% only which was significantly lower compared to that of step 2 (p<0.001), thus indicating minimal role of adjuvant drugs that this step could be skipped for the next step. Yet, adjuvant drugs were found to be valuable for patients who did not respond to step 2 or step 3 alone, 11.4% in step 2 and 50% in step 3 responded well after addition of adjuvant drugs**.**

In the present study, 95.3% patients of cancer cervix with pain, responded to WHO guided pain management protocol. Grand etal (1993) reported that WHO guided pain management protocol provided adequate analgesia in 95% of patients with camcer pain. Gayatri Palat etal (1993) in a study reported that pain in cancer cervix patients could be managed effectively in about 80-90% of patients. C S Cleeland et al (2005), in an inter group study , coordinated by Eastern cooperative oncology group, registered 225 patients of cancer pain. 43% were given milder opiod (codeine) and 24% received stronger opiod (morphine). they reported 66% relief provided by medication. Of 4 non-responders in step 3, 2 (50%) showed response on adjuvants while remaining 2 (50%) did not respond. This prompts us to look for a better adjuvant therapy in order to get the absolute response at final stage of the protocol. Progression of disease stage showed response to higher steps of pain relief in WHO step ladder protocol ('p' = 0.0001). 75.4 % patients amongst stage 2 were relieved at step 1 compared to only 24 % of patients amongst stage 3. 30.7% patients in stage 3 needed step 2 and 44% needed step 3. majority of patients in stage 4 (80%) were relieved only after step 3.

CONCLUSION

This WHO guideline implementation study supports the use of algorithm for cancer pain management. Effective pain relief was achieved in 95.3 % of our patients with minimal side effects that could be easily managed. Pain management using WHO algorithm must be an integral part of management of cancer cervix patients throughtout the world.

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