Efficacy of pre-operative oral pregabalin use on postoperative pain in total knee replacement:

INTRODUCTION:

Total knee arthroplasty is among the most common orthopaedic surgeries that is being performed to relieve joint pains in patients who had advanced osteoarthritis and rheumatoid arthritis [(1)]. This procedure is associated with moderate to severe postoperative pain which requires pre-emptive planning of multimodal analgesia. Although Opioids are the mainstay treatment for postoperative acute pain management, they are associated with adverse side effects which limit postoperative rehabilitation, reduce patient satisfaction and overall outcome.

Opioids are well documented for their adverse effects, especially in geriatric patients presenting for Orthopaedic surgeries. The tolerance and physical dependence can develop at prescribed doses even[(2)]. Opioids are associated with sedation, respiratory depression, paralytic ileus, immunosuppression and opioid-induced endocrinopathy to name a few.

Pregabalin is analogue of neurotransmitter gamma-aminobutyric acid (GABA)[(3)]anticonvulsant and has wide range of clinical uses which encompass treatment of not only seizures but also neuropathic pains, adjuvant analgesia in general anaesthesia as part of multimodal analgesia plan, to limit Opioids use. It mainly acts through binding on alpha-2 and delta receptors and act as antihyperalgesic agent [(4)]. Pregabalin delays or offsets the sensitization of dorsal horn neurons, possibly leading to augmentation of surgical stimulation that affects changes in the central and peripheral nervous system.

Postoperative pain of Total knee replacement and total Hip replacement has profound effects on patient rehabilitation and satisfaction postoperatively. Mohsen Ziyaeifard et el had studied its effects in patients undergoing CABG that showed its safety profile along with opioid sparing properties. [(5)]

Multimodal analgesia is a term that encompass more than one intervention simultaneously to aim multiple receptors within nociceptive and neuropathic pathways to control postoperative pain by providing opioid-free or opioid-reduced anesthesia. This includes regional anesthesia as core component. Femoral nerve block is one standard intervention which has documented

analgesia for lower limb surgeries with wide range of safety profile. It reduces the incident of chronic postoperative pain as well.[6]

In all efforts to develop an opioids free or opioid reduced anesthesia practice, we try to use adjuvants in our practices to improve the outcome without adverse effects. One such practice is addition of Dexmedetomidine in femoral nerve block to enhance the postoperative analgesia duration and quality. Qianchuang Sun et el meta-analysis has shown that dexmedetomidine prolongs the duration of Tap block as well as improve the quality of analgesia[7].Another study reported 30% increase in duration of ulnar nerve block with IV dexmedetomidine, and 100% increase in duration of ulnar nerve block with perineural treatment[8], compared with an identical doseof ropivacaine alone. Dexmedetomidine is alpha-2 adrenoceptor agonist who act centrally and produce sedative and analgesic effects without respiratory depression or paralytic ileus.[9]

OBJECTIVE:

To evaluate efficacy and safety of perioperative Oral pregabalin 75mg in improving postoperative pain control in patients undergoing total knee replacement surgeries under regional anesthesia.

HYPOTHESIS:

Pre-operative oral pregabalin reduces postoperative pain, analgesia and opioid requirement.

MATERIAL AND METHODS:

STUDY TYPE: **Interventional (Randomized control trial)**

PRIMARY PURPOSE: Treatment

STUDY SETTING: Operation Theatres, Bahrain defence forces

DURATION OF STUDY: 12-18months after the approval of protocol

POPULATION: Patients scheduled for Total knee arthroplasty

ALLOCATION: Balanced randomization of separate strata will be done according to age and pre-morbid conditions with computer software win-pepi ETCTERA procedure that randomly allocates the subjects to 2-8 groups (treatment / control using random

numbers making relative sizes of the groups (in each stratum as close as possible to what is needed the subjects in each stratum. (Annexure III attached).

MASKING: Single blinding procedure will be adopted

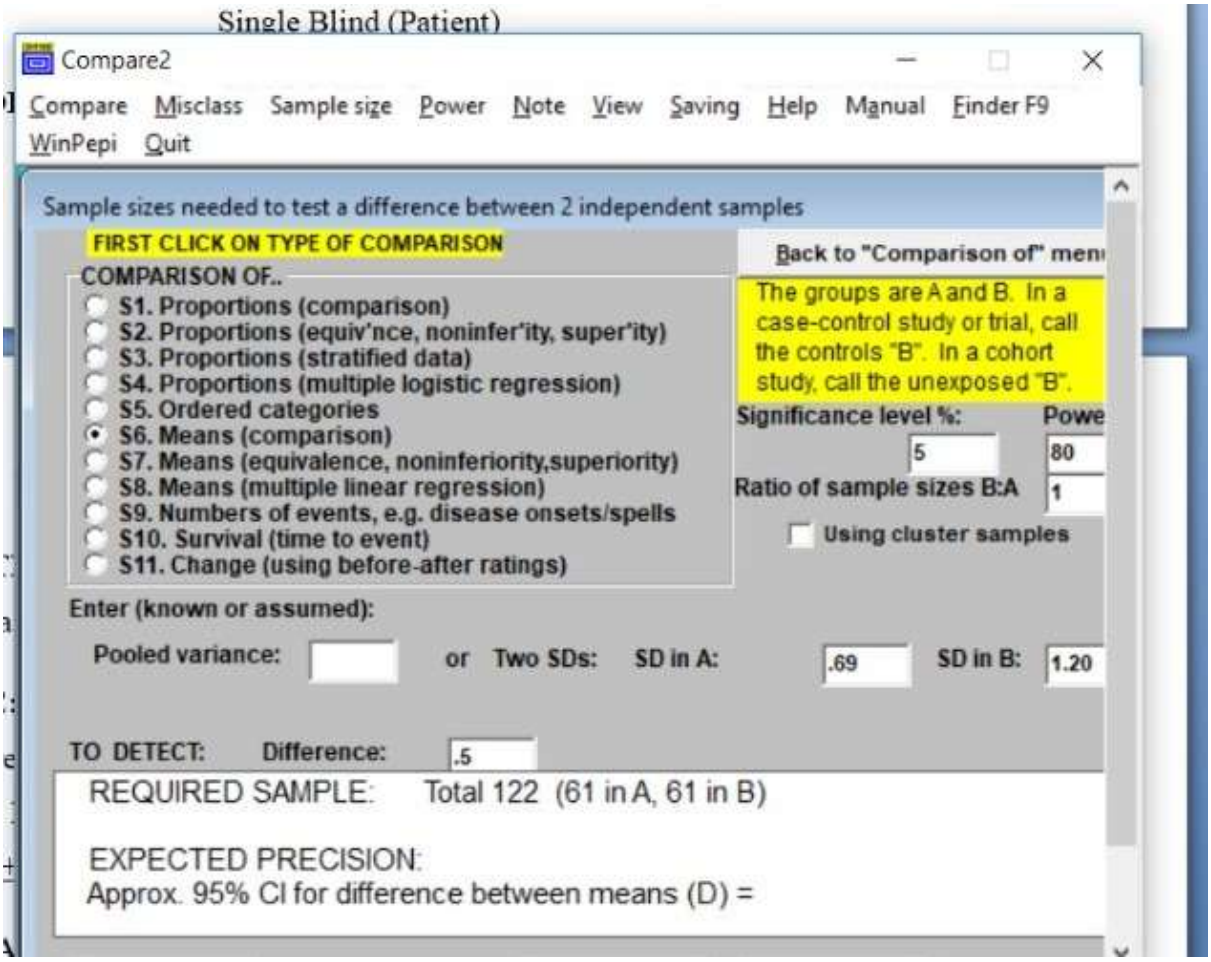
COMPARATOR: None

OFFICIAL TITLE: Effect of Pre-operative oral pregabalin in Total Knee replacement for postoperative pain. A randomized Controlled Single blind trial.

SAMPLE SIZE: Sample size calculated with win-pepi ver: 11.15 for comparision of mean with 80% power of test, 5% level of significance and assuming means $\pm$ SD of static pain score in Group B (prgablin) = 2.2 $\pm$.69 and means $\pm$ SD of static pain score in Group A (conrol) = 3.5 $\pm$ 1.20.

REQUIRED SAMPLE: Total 122 (61 in A, 61 in B)

(From study of Jain P, Jolly A, Bholla V, Adatia S, Sood J. Evaluation of efficacy of oral pregabalin in reducing postoperative pain in patients undergoing total knee arthroplasty. Indian J Orthop. 2012 Nov;46(6):646-52)



Inclusion criteria:-

1. Age between 40 to 85 year
2. All patients scheduled for Total knee replacement.
3. Elective Regional anaesthesia.
4. Able to follow study protocol
5. Patients with CRF stage1-3 (Dose modification applicable)

Exclusion Criteria:

1. ASA –IV (Annexure IV attached)
2. Age <40 &> 85 years
3. Patients on pregabalin for chronic neuropathic pain.
4. Patient under General anesthesia

5. Patients with chronic liver failure
6. Patients with chronic renal failure stage 4 on Haemodialysis
7. Patients on opioid (>3 month)
8. Patient with complicated knee surgery.

DATA COLLECTION PROCEDURE:

After obtaining approval from the institutional ethical committee and informed written consent, 122 patients fulfilling the inclusion criteria will be included in this study. After approval from ethical review board and informed consent. Balanced allocation of 122 subjects to groups A and B: (relative sizes 1:1): randomly assigned into two parallel equal groups using a balanced randomization based on age and pre-morbid conditions through a computer software win-pepi ver: 11.16 / ETCETRA. (Annexure III). Single blinding i.e. of subjects will be done for receiving preoperative pregablin. Since control group is receiving standard post operative analgesia no further intervention will be given for treatment.

Intra operatively both groups will receive inj. Midazolam 2 mg before subarachnoid block with hyperbaric Bupivacaine 0.5%2.5-3ml and fentanyl 15mcg in the operation theatre (OT). Both groups will also receive parecoxib 40mg IV and paracetamol 1G Intravenous (IV) as part of multimodal analgesia. Both groups will receive dexamethasone 8mg IV prophylactically.

Postoperatively both group will receive Ultrasound guided Adductor canal saphenous Nerve block in the PACU with 0.2% Bupivacaine 20-30ml & dexmeditomidine1.0mcg/kg. Group B will receive oral capsule pregabalin 75 mg Q12hrly from the 1st dose for next 60 hrs. Group A will not receive Pregabalin. Both groups will receive paracetamol 1G IV Q6Hrly for 24 hrs and rescue Analgesia will be provided with oral oxycodone 5mg TDS as PRN and Morphine PCA, in escalating manner as per patient requirement.

After 24 hrs both group will continue with paracetamol 1G Q6Hourly and tab Ibuprofen 400mg Q8 Hourly along with oxycodone or PCA morphine as per requirement for 72 hrs. (Post op analgesia plan for 72 hrs is attached for review)

DATA ANALYSIS:

Data will be entered and analyzed in using computer software SPSS version 20.0. Quantitative variables like VAS, RASS score will be described as mean +SD. Qualitative variables like outcome (incidence of bradycardia, hypotension, PNOV(will be described in frequency and percentage, Outcome will be compared among two groups using independent T test for numerical variables (VAS, RASS score) and chi-square for nominal variables i.e. incidence of bradycardia, hypotension, PNOV (yes / no) with p value of ≤ 0.05 will be considered statistically significant.

Outcome measure:

Primary outcome:

- VAS score at 4hrs, 8hrs, 12hrs, 24hrs, 36 hrs, 48hrs, 60hrs, and 72hrs. Annexure attached

Secondary outcome:

- Sedation score: RASS score at4hrs, 8hrs, 12hrs, 24hrs,36 hrs, 48hrs, 60hrs, 72hrs.Annexure attached
- VAS at 1st CPM :
- Time of 1st analgesia request
- Incident of bradycardia in 1st 24 Hrs
- Incident of Hypotension in 1st 24 Hrs
- Incident of PONV in 1st 24 hrs
- Total opioid consumption in 72hrs: Oxycodone/Morphine
- Patient satisfaction at 72 hrs : rated as numeric 1-5 (1=not satisfied, 5=fully satisfied)

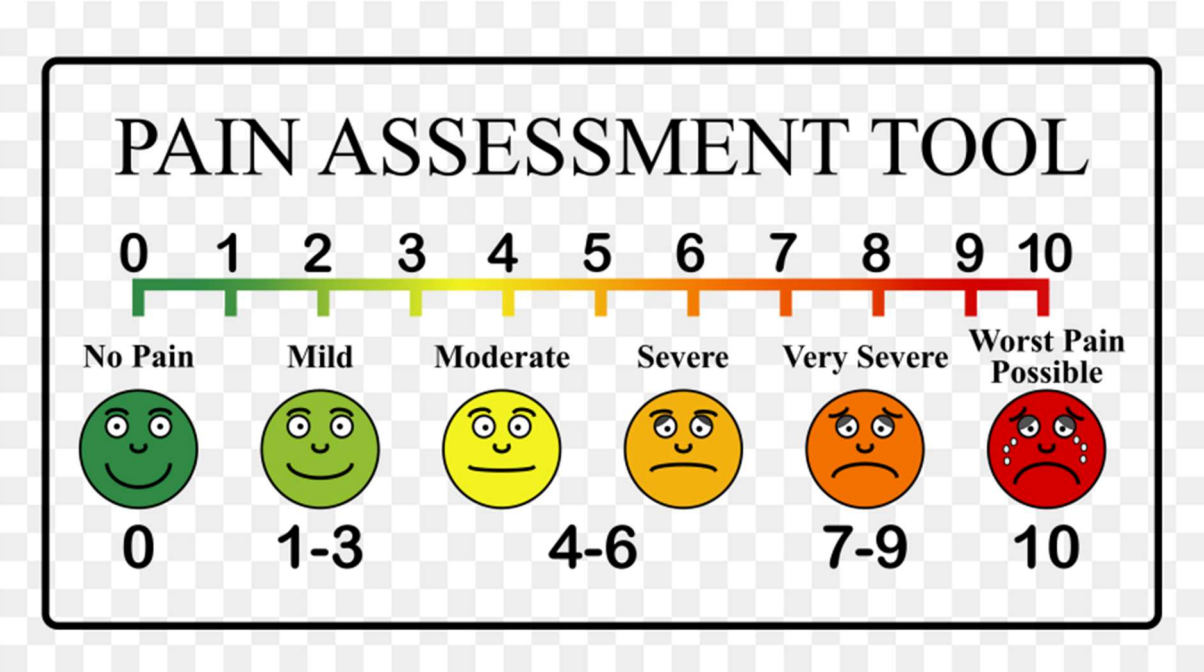
ETHICAL CONSIDERATION:

According to international guidelines, though its low risk research with risks to study participants are minimal an informed consent will be taken, Data confidentially will be maintained at every stage of trial. All the data will be stored in principal investigator computer with password. Subjects will be explained the nature of research protocol and data collection

procedure. Randomization of subjects will be done and principal investigator believes that the research literature shows that there exists a state of equipoise an honest professional disagreement' among medical scientists about which treatment a randomization does not harm trial participants because it constitutes a 'fair bet' procedure among outcomes that are *a priori* equally valuable. Single blinding procedure will be adopted. The patients will be informed about the investigational drug, that the drug is part of their multimodal analgesia plan but it may or may not be included.

ANNEXURE I:

VAS score



ANNEXURE II:

RASS score

The Richmond Agitation–Sedation Scale		
Score	**Term**	**Description**
+4	Combative	Overtly combative or violent; immediate danger to staff
+3	Very agitated	Pulls on or removes tube(s) or catheter(s) or has aggressive behaviour toward staff
+2	Agitated	Frequent non purposeful movement or patient–ventilator dyssynchrony
+1	Restless	Anxious or apprehensive but movements not aggressive or vigorous
0	Alert and calm	Spontaneously pays attention to caregiver
-1	Drowsy	Not fully alert, but has sustained (more than 10 seconds) awakening, with eye contact, to voice
-2	Light sedation	Briefly (less than 10 seconds) awakens with eye contact to voice
-3	Moderate sedation	Any movement (but no eye contact) to voice
-4	Deep sedation	No response to voice, but any movement to physical stimulation
-5	Unarousable	No response to voice or physical stimulation

ANNEXURE III:

Balanced allocation (in 2 strata) to groups A (control) and B (pregabalin)

Stratum 1: Age group (40-62 year) stratum 2: Age Group (63-85)

(Relative sizes of groups: 1:1).

STRATUM 1:

1: P 2: C 3: P 4: P 5: P 6: P 7: C

8: P 9: P 10: P 11: P 12: P 13: C

14: P 15: C 16: C 17: P 18: P 19: P

20: P 21: C 22: P 23: C 24: C 25: C

26: P 27: P 28: C 29: C 30: C 31: C

32: C 33: C 34: C 35: P 36: P 37: C

38: C 39: P 40: P 41: P 42: C 43: P

44: C 45: P 46: C 47: P 48: P 49: C

50: C 51: C 52: P 53: C 54: P 55: C

56: P 57: C 58: C 59: C 60: C 61: P

Totals:

Group C: 30

Group P: 31

STRATUM 2:

1: P 2: C 3: P 4: P 5: P 6: P 7: P

8: C 9: P 10: C 11: P 12: C 13: P

14: P 15: C 16: C 17: C 18: P 19: P

20: P 21: C 22: C 23: P 24: C 25: P

26: C 27: P 28: P 29: C 30: P 31: P

32: P 33: C 34: C 35: P 36: P 37: P

38: C 39: P 40: P 41: C 42: C 43: P

44: C 45: C 46: C 47: C 48: C 49: P

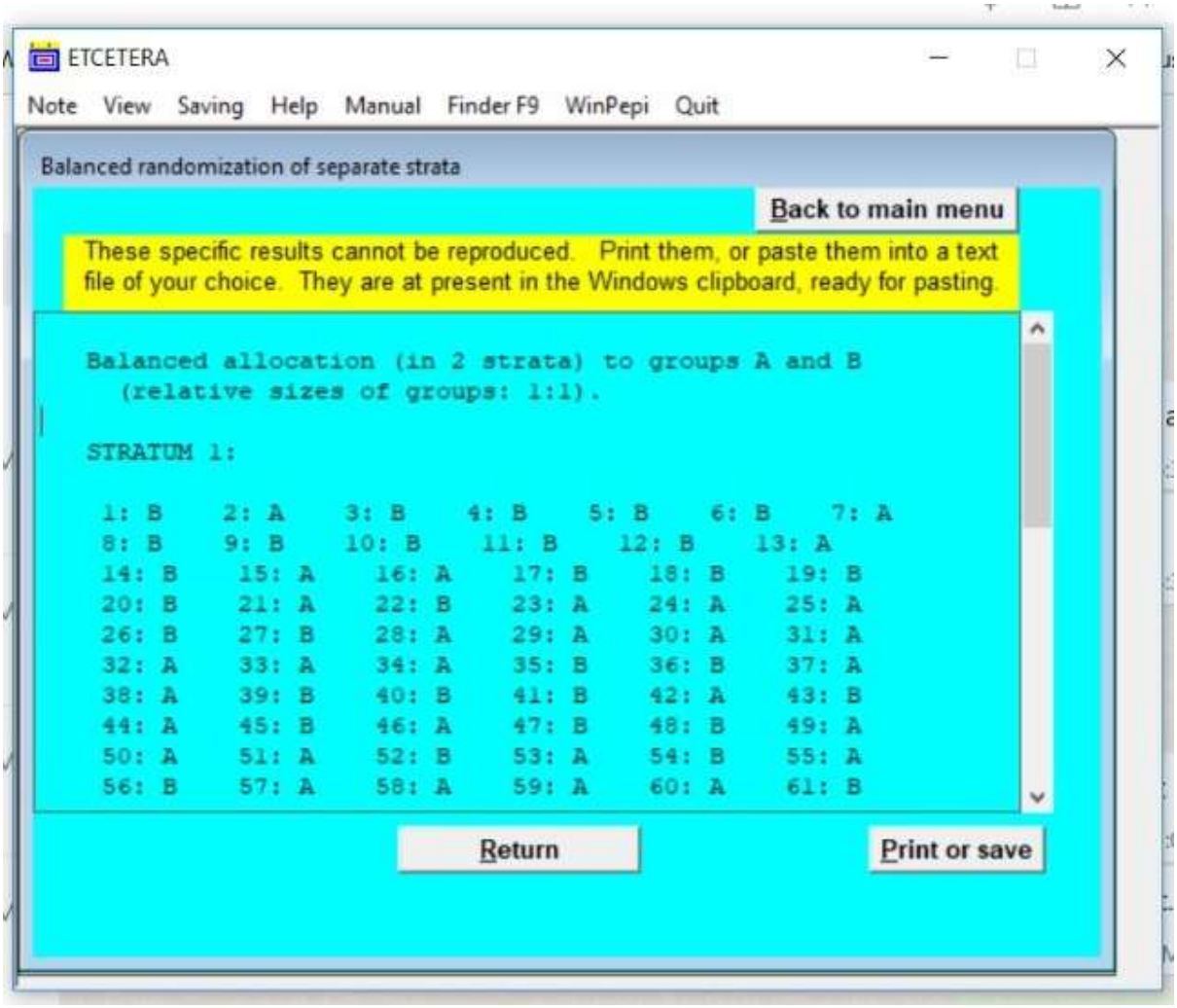
50: P 51: C 52: P 53: C 54: C 55: C

56: C 57: C 58: C 59: P 60: C 61: C

Totals:

Group C: 31

Group P: 30


ETCETERA
Note View Saving Help Manual Finder F9 WinPepi Quit
Balanced randomization of separate strata
Back to main menu
These specific results cannot be reproduced. Print them, or paste them into a text file of your choice. They are at present in the Windows clipboard, ready for pasting.
Balanced allocation (in 2 strata) to groups A and B
(relative sizes of groups: 1:1).
STRATUM 1:
1: B 2: A 3: B 4: B 5: B 6: B 7: A
8: B 9: B 10: B 11: B 12: B 13: A
14: B 15: A 16: A 17: B 18: B 19: B
20: B 21: A 22: B 23: A 24: A 25: A
26: B 27: B 28: A 29: A 30: A 31: A
32: A 33: A 34: A 35: B 36: B 37: A
38: A 39: B 40: B 41: B 42: A 43: B
44: A 45: B 46: A 47: B 48: B 49: A
50: A 51: A 52: B 53: A 54: B 55: A
56: B 57: A 58: A 59: A 60: A 61: B
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9. Dexmedetomidine as an Adjuvant in Peripheral Nerve Block, Zheping Chen,1 Zhenzhen Liu, Chang Feng, Yanwu Jin, and Xin Zhao.
doi: 10.2147/DDDT.S405294

Case report form:

Effect of Perioperative oral pregabalin in Total Knee replacement for postoperative pain.

Serial N0: _____ Hospital Record NO: _____

Date: _____ Patient Age: _____

Gender: _____ ASA Status:_____

Preoperative Oral capsule pregabalin time: _____.

Subarachnoid block given (Bupivacain+fentanyl) (Start point time) _____

Postoperative USG guided femoral nerve block (Bupivacaine +dexmedetomidine): start point time. _____

VAS SCORE :(0-10)

Time:Start point	At 4Hrs	8Hrs	12Hrs	24Hrs
	36 Hrs	48Hrs	60Hrs	72Hrs

Sedation score: RASS attached {0- (-5)}

+4	+3	+2	+1	0	-1	-2	-3	-4	-5

Time:Start point	At 4Hrs	8Hrs	12Hrs	24Hrs
	36 Hrs	48Hrs	60Hrs	72Hrs

VAS at 1st CPM : _____

Time of 1st analgesia request:_____

Incident of bradycardia in 1st 24 Hrs: Y/N _____

Incident of Hypotension in 1st 24 Hrs: Y/N _____

Incident of PONV in 1st 24 hrs: Y/N _____

Total opioid consumption in 72hrs: Oxycodone: _____mg Morphine: _____ mg.

Patient satisfaction (1-5):at 72 Hrs(1: Not satisfied, 5: fully satisfied)

1	2	3	4	5

ANNEXURE IV

ASA STATUS

ASA I
Patients are considered to be normal and healthy. Patients are able to walk up one flight of stairs or two level city blocks without distress. Little or no anxiety. Little or no risk

ASA II
Patients have mild to moderate systemic disease or are healthy ASA I patients who demonstrate a more extreme anxiety and fear toward dentistry. Patients are able to walk up one flight of stairs or two level city blocks, but will have to stop after completion of the exercise because of distress. **Examples**: History of well-controlled disease states including non-insulin dependent diabetes, prehypertension, epilepsy, asthma, or thyroid conditions; ASA I with a respiratory condition, pregnancy, and/or active allergies. May need medical consultation.

ASA III
Patients have severe systemic disease that limits activity, but is not incapacitating. Patients are able to walk up one flight of stairs or two level city blocks, but will have to stop enroute because of distress. If dental care is indicated, stress reduction protocol and other treatment modifications are indicated. **Examples:** History of angina pectoris, myocardial infarction, or cerebrovascular accident.

ASA IV
Patients have severe systemic disease that limits activity and is a constant threat to life. Patients are unable to walk up one flight of stairs or two level city blocks. Distress is present even at rest. Patients pose significant risk since patients in this category have a severe medical problem of greater importance to the patient than the planned dental treatment. **Examples**: History of unstable angina pectoris, myocardial infarction or cerebrovascular accident within the last six months, severe congestive heart failure.

ASA V
Patients are moribund and are not expected to survive more than 24 hours with or without an operation. These patients are almost always hospitalized, terminally ill patients. Elective dental treatment is definitely contraindicated; however, emergency care, in the realm of palliative treatment may be necessary.

ASA VI
Clinically dead patients being maintained for harvesting of organs.

ASA-E: Emergency operation of any variety (used to modify one of the above classifications, i.e., ASA III-E).

* Status can change as medical history changes; adapted by Margaret J. Fehrenbach, RDH, MS, from the American Society of Anesthesiologists, *Medical Emergencies in the Dental Office* (Malamed, Mosby, 2008), and included in *Saunders Review of Dental Hygiene* (Fehrenbach and Weiner, Elsevier, 2009).