JACR-22-14863

Pre-emptive Analgesia for the Prevention of Chronic Postsurgical Pain: A Systematic Review and Meta-analysis with Trial Sequential Analysis

Endale Gebreegziabher Gebremedhn[1*], **Worku Mekonnen Sefefe**[2]

[1]*Department of Anaesthesia, University of Gondar, Ethiopia;* [2]*Department of surgery, University of Gondar, Ethiopia*

Correspondence to: Endale Gebreegziabher Gebremedhn, Department of Anaesthesia, University of Gondar, Ethiopia, Tel: 251955220458; E-mail: gebaw21@gmail.com

SUPPLEMENTARY MATERIAL

Study	**Sample size at different times**	**Pre-emptive analgesia**	**Dose, route and time drug given**		**Surgery**	**Pain assess-ment**	**Primary outcome: presence of postsurgical pain at>3 months.**	**Secondary outcome**
			Treatment group	**Control/ active treatment group**				
Grigoras et al.	T=17 C=19	Lidocaine	B=1.5 mg/kg IV followed by INF=1.5 mg/kg IV, after ETTI and stopped 60 minutes after skin closure	Received an equivalent saline.	Breast surgery	MPQ, VAS (0-10)	At 3 months: CPSP: lidocaine *vs.* 2 (11.8%) *vs.* control 9 (47.4%) (*P*=0.031).	At 3 months: Worse pain during moment lidocaine *vs.* controls 0(0%) *vs.* 8 (41.2%) (*P*=0.003). Overall intensity of pain (mean ± SD): 0.2 (± 0.5) *vs.* 0.9 (± 1.4) (P=0.023). Hyperalgesia lidocaine

								vs. control (mean ± SD): 0.2(± 0.8) ***vs.*** 3.2(± 4.5) (P= 0.002).
Lavand'homme *et al.*	T=20/20/20/20	Ketamine	G3=EPI-EPI: Ketamine= 0.5 mg/kg IV bolus 30 minutes before skin incision followed by epidural 0.25 mg/kg/hr till end of surgery	G1=IV-IV G2=IV-EPI G4=EPI-IV	Digestive surgery	VAS (0-10)	6 months: Patients treated with preop bolus ketamine G1: 10 (51%), G2:2 (10%), G3:0 (0%) and G4:0 (0%) (P<0.01). 12 months: G1:6 (28%), G2: 2 (11%), G3:0 (0%) and G4:0 (0%) (P<0.05) developed pain.	At 6 months: treatment group (G3) 1 (5%) ***vs.*** group 2: 2 (10%) and group 4: 3 (15%) patients developed back pain.
Jahangiri et al.	T=13 C=11	Epidural infusion: diamorphine, bupivacaine, clonidine	INF: diamorphine=5 mg; bupivacaine =75 mg and clonidine=150 µgm (24-5 hrs before surgery)	Received on demand opioids	Lower limb amputation	VAS (0-10)	Phantom pain at 6 months in controls 9 (72.7%) ***vs.*** study groups 3 (7.7%) (*P*=0.002) and 12 months in controls 8 (72.7%) ***vs.*** study groups 2 (7.7%) (*P*=0.002).	-
Suzuki et al.	T=22 C=22	Epidural plus Ketamine (IV) -Epidural plus saline	Ketamine=0.05 mg/kg/hr IV infusion after ETTI on top of epidural that	Saline IV infusion on the top of epidural	Thoracotomy	NRS	3 months: Fourteen (58.3%) patients from the control group and 7 (28%)	At 3 months (n=14; *P*=0.56): heavy pain from the wound ketamine 6

			continued for 3 days postoperatively				patients from ketamine group experienced pain (NRS ≥ 1) (*P*=0.03). Nine (37.5%) patients from the control group and 2 (8%) patients from ketamine group received medication for pain control (*P*=0.03). 6 months: Sharp pain: ketamine 0 (0%) and control 3 (13.6%) patients.	(27.3%) and control 9 (40.9%) patients. Sharp pain: ketamine 0 (0%) and control 1 (4.5%) patients. At 6 months (n=12; *P*=0.4): heavy pain ketamine 7 (31.8%) and control 8 (36.4%) patients. Tingling: ketamine 5 (22.7%) and control 6 (27.3%) patients.
Salengros et al.	T=18 C=20	Low dose remifentanil with epidural with 0.5% ropivacaine	Low dose remifentanil IV infusion **(**average effect site concentration 1.99 _ 0.02 ng/mL) with epidural (0.5% ropivacaine)started at the beginning of anaesthesia	High-dose remifentanil IV infusion **(**average effect-site concentration 5.61 _ 0.84 ng/mL) with epidural started at the end of surgery	Thoracotomy	DN4 neuropathic pain diagnostic questionnaire	Numbers of patients experienced pain (remifentanil): -3 months: high dose 15/20 (75%) ***vs.*** low dose 5/18 (27.8%) (P=0.013) -6 months: high dose 16/20 (80%) ***vs.*** low dose 5/18 (27.8%) (P=0.008) -13 months:	NRS at 3 months (mean ± SD): High-Dose Group: 3.00 ± 1.51 and low dose: 2.43 ± 1.62 (P=0.42). NRS at 6 months (mean ± SD): high dose: 2.88 ± 1.36 and low dose: 3.50 ± 2.28 (P=0.67). At 13 months (mean ± SD): high dose: 2.28

							high dose 14/20 (70%) *vs.* low dose 3/18 (16.7%) (P=0.009)	± 1.33 and low dose: 4.33 ± 2.08 (*P*=0.10).
Obata et al.	T=28 C=30	Thoracic epidural	4 ml of 1.5% mepivacaine bolus started 20 minutes before skin incision followed by 4 ml/hr infusion until 72 hrs after operation	4 ml of 1.5% mepivacaine bolus started at the end of surgery followed by 4 ml/hr infusion until 72 hrs after operation	Thoracotomy	NRS	3 months: 14 (50%) and 23 (77%) patients developed long-term pain in pre-group and post group respectively. 6 months: In pre-group 9 (33%) and post group 20 (67%) patients developed long-term pain.	At 3 months: In pre-group 11% and in post group 23% patients took medication for pain control. 6 months: The NRS was lower in the Pre group at 6 months after operation (P=0.015). Whereas 4% and 6% patients took medication for pain control from pre and post groups respectively
Karanikolas et al.	T=13/13/13/13 C=13	Epidural/PCA	Epi/Epi/Epi: bupivacaine, 2 mg/ml, and fentanyl, 2 µg/ml, infusion at 4–8 ml/h), started before 48 hrs of surgery. PCA/Epi/Epi: IV	Received conventional analgesia	Limb amputation	VAS, MPQ-PRIR	At 6 months: PLP prevalence: Epi/Epi/Epi 1 (7.7%), PCA/Epi/Epi 4 (30.7%), PCA/Epi/PCA 7 (58.3%) and PCA/GA/P	

			fentanyl 25 µg; lockout, 20 min; and no basal infusion) for 48 h and also received epidural normal saline at 2 ml/h. PCA/GA/PCA: IV fentanyl 25 µg; lockout, 20 min; no basal infusion), started at 48 h before surgery.				CA 3 (23%) groups compared to the control group 9 (75%) (P=0.004). PLP VAS score: median (minimum-max): Epi/Epi/Epi 0 (0-20), PCA/Epi/Epi 0 (0-42), PCA/Epi/PCA 20 (0-40), PCA/GA/PCA 0 (0-30) and control 20 (0-58) (P=0.001).	
Comez et al.	T=20/20 C=20	-Epidural (PE) -Epidural + Dexketoprofen (PED)	Epidural (PE): 10-15 ml of 0.125% levobupivacaine before 5 minutes of anaesthesia. Epidural + Dexketoprofen (PED): 10-15 ml of 0.125% levobupivacaine before 5 minutes of anaesthesia. Dexketoprofen 50 mg in 100 m normal saline IV infusion before 15 minutes of skin incision.	No preoperative analgesia was given	Thoracotomy	VAS	6 months: The incidence of post thoracotomy chronic pain in PED 2 (10%), PE 4 (20%) and Control 6 (30%). The VAS score (mean ± SD) control group: 1.85 ± 1.496 *vs.* PE: 1.15 ± 1.348 *vs.* PED: 0.60 ± 1.142 (P=0.017).	6 months: Patient satisfaction score: control 9 (45%) *vs.* PE 11 (55%) *vs.* PED 18 (90%) (P=0.008).

Kairaluoma et al.	T=30 C=30	Paravertebral nerve block (PVB)	0.5% bupivacaine of 1.5 mg/kg injected at T3 before anaesthesia.	Received saline subcutaneously at the corresponding puncture site	Breast surgery with axillary dissection	NRS	6 months: the prevalence of pain symptoms (tactile stimulus: median/range) was lower in PVB: 0.5 (0-3) *vs*. sham group 1 (0-4) (*P*=0.029). 12 months: prevalence of pain symptoms: control 23 (77%) *vs.* PVB 13 (43%) (*P*=0.008)	At 12 months NRS median (range): motion related pain: PVB 0 (0–6) *vs.* 2 (0–8) (P=0.003). Pain at rest: PVB 0 (0–1) *vs.* control 0 (0–8) (P=0.011).
Dertwinkel et al.	T=25 C=28	Ketamine	KG=0.5 mg/kg IV bolus immediately after induction of anaesthesia, followed by 0.003 mg/kg/24 hr IV infusion and 0.001 mg/kg/48 hr IV infusion	Not received perioperative ketamine	Amputation of limbs	NRS	9 months: KG one patient (9.1%) and control group 10 (71.4%) patients developed severe phantom limb pain (P=0.01).	9 months: Seven (63.6%) and 11 (78.5%) patients developed chronic phantom limb pain in ketamine and control groups respectively.
Xu et al.	T=62 C=79	Celecoxib, tramadol and acetaminophen	Celecoxib= 200 mg BID orally, tramadol 37.5 mg orally and acetaminophen 325 mg orally TID 72-1 hr before surgery.	No drug was given to the control group preoperatively	Total knee arthroplasty	VAS	There was low VAS score during moment at 3 months in treatment group compared to the control group (P=0.012)	-

Remerand et al.	T=72 C=70	Ketamine	B=0.5 mg/kg IV before skin incision, followed by 2 µgm/kg/min for 24 hour infusion	Saline bolus, followed by saline	Total hip arthroplasty	NRS	6 months: Ketamine group 6 (8%) and placebo group 15 (21%) patients experienced pain at rest (P=0.036).	6 months: 3 (4.2%) from ketamine group and 10 (13.3%) placebo group reported their pain NRS>3 at rest (P=0.04).
Senturk et al.	T=22 C=24/23	Thoracic epidural analgesia (TEA)	Pre-TEA: bolus of 10 ml of 0.1% bupivacaine plus 0.1 ml morphine 30 minutes before anaesthesia, followed by 7 ml/hr infusion of the same solution during operation.	In Post TEA group, no epidural medication was applied until the postoperative period	Thoracotomy	NRS	At 6 months: Pre-TEA 10 (45%), Post-TEA 15 (63%) and IV-PCA 18 (78%) (P<0.05).	6 months: The NRS scores (mean±SD) were Pre-TEA (0.6 ± 0.8), Post-TEA (0.9 ± 0.9) and IV-PCA (1.4 ± 1.2)
Khurana et al.	T=30/30 C=30	Gabapentin, pregabalin	Gabapentin =300 mg orally and Pregabalin= 75 mg orally before 1 hr of surgery and every 8 hr for 7 days postoperatively	Received placebo before 1 hr of surgery	Spinal surgery	VAS	3 months: VAS score (mean) in pregabalin group was significantly low compared with gabapentin and placebo group (P<0.05).	Prolo functional score: excellent score gabapentin 3 (10%), pregabalin 13 (43.3%) and placebo group 9 (30%) ODIS: moderate disability gabapentin 13 (43.3%), pregabalin 3 (10%) and placebo 14 (46.7%).

Buvanendran et al.	T=113 C=115	Pregabalin	Pregabalin 300 mg orally 1-2 hr before surgery	Received matched placebo tablet orally 1-2 hr before surgery	Total knee arthroplasty	NRS	3 months: neuropathic pain in pregabalin group 0 (0%) *vs.* placebo 10 (8.7%) (P=0.001). 6 months: the incidence of neuropathic pain in pregabalin 0 (0%) *vs.* placebo 6 (5.2%) (P=0.014).	3 months: allodynia on operated leg was low in pregabalin group 2 (2%) *vs.* placebo group 14 (12%) (P=0.002). 6 months: allodynia on operated leg was low in pregabalin group 0 (0%) *vs.* placebo group 9(8%) (P=0.002).
Amr et al.	T=50/50 C=50	venlafaxine	Venlafaxine =37.5 mg/day and gabapentin 300 mg/day orally the night before surgery and for 10 days postoperatively	Received placebo the night before surgery and for 10 days postoperatively	mastectomy	VAS	6 months: stabbing/pricking pain significantly reduced in venlafaxine group 7 (14%) compared to the control group 20 (40%) (P=0.003) and gabapentin group 16 (32%) (P=0.028). Burning pain was also significantly reduced in venlafaxine group 1(2%)	6 months: more patients used opioids in the control group 18 (36%) (P=0.02) and gabapentin groups 17 (34%) compared to venlafaxine group 8 (16%) (P=0.03)).

							compared with the control group 11 (22%) (P=0.0018) .	
Bouzia et al.	T=31/31 C=31	pregabalin	Group2: Pregabalin= 75 and Group3: 150 mg orally before surgery.	Group1: Placebo capsule orally before surgery	Cardiac surgery	VRS	3 months: analgesia consumption group1: 26/31, group2: 16/31 and group3: 10/31 (P <0.001)	3 months: VAS score: median (minimum, max): Control 3 (2, 5), group2: 2 (1, 3) and group3: 2 (1, 3) (P<0.001). sleep disturbance group1: 16/31, group2: 5/31 and group3: 3/31 (P <0.001).
Sen et al.	T=20/20 C=20	Ketamine and pregabalin	Ketamine group: placebo capsule, 0.3 mg/kg IV bolus and 0.05 mg/kg/hr infusion before skin incision until the end of operation. Pregabalin group=1.2 gram orally and bolus plus infusion of saline 1 hr before skin incision	Placebo capsule and bolus plus infusion of saline	hysterectomy	VRS	3 and 6-months:the incidence of incisional pain and pain scores were significantly lower in the gabapentin group compared with the ketamine and control groups (*P* <0.001)	-

Brogly et al.	T=23 C=24	Gabapentin	Gabapentin =1200 mg orally 2 hr before surgery	Placebo orally 2 hr before surgery	thyroidectomy	DN2	6 months: DN2 score was significantly reduced in gabapentin group 1 (4.3%) compared to the placebo group 7 (29.2%) (P=0.04).	-
Ju et al.	T=50/48/38 C=48/43/39	Epidural	Epidural: initiated before skin incision and maintained with 5-10 ml/hr 0.5% ropivacaine during operation	Cryo group: each intercostal nerve exposed at the end of surgery and received 90 seconds application of cold (-70 C^0)	Thoracotomy	VRS	3 months: moderate to severe pain epidural 4 (8%) *vs.* cryo group 11 (22.9%) (P=0.077). 6 months: severe to moderate pain- epidural 3 (6.3%) and cryo group 12 (27.9%) (P=0.013) 12 months: moderate to severe pain epidural 2 (5.3%) *vs.* cryo group 9 (23.1%) (P=0.056).	Allodynia like pain: 6 months: epidural 1(2.1%) and cryo 6 (16.3%) (P=0.044). 12 months: epidural 0 (0%) and cryo 6 (15.4%) (P=0.025). Interference with daily life: 3 months: epidural 6 (12%) and cryo 18 (37.5%) (P=0.003). 6 months: epidural 5 (10.4%) and cryo 15 (34.9%) (P=0.005). 12 months: epidural 3 (7.9%) and cryo 13 (33.3%) (P=0.014).
Sen et al.	T=30 C=29	gabapentin	Gabapentin 1.2 gm orally 1 hr before surgery	A placebo capsule was taken orally 1 hr before surgery	Herniorrhaphy	VAS	3 and 6 months: the mean VAS score was lower in	-

							gabapentin (1.25) group compared with the placebo group (2.5) (P< 0.05).	
Fassoulaki et al.	T=22/20 C=22/21	Gabapentin	Gabapentin 400 mg orally starting the night before the day of surgery and 8 days postoperatively	Placebo capsules orally starting the night before the day of surgery and 8 days postoperatively	Breast surgery	VAS	3 months: 18/22 (82%) patients in control group and 10/22 (45%) patients in the treatment group developed chronic pain (P=0.028). 6 months: 12/21 (57%) patients from control and 6/20 (30%) patients from treatment developed chronic pain (P=0.151).	3 months: Axillary pain 10 (22%) patient from control and 3 (14%) patients from treatment group (P=0.045). Arm pain 13 (59%) patients from control and 5 (22%) patients from treatment groups (P=0.038). Five (23%) patients from control and 0 (0%) patients from treatment (P=0.048) needed analgesia. 6 months: Four/21 (21%) patients from the control and 0/20 (0%) patients the treatment groups needed analgesia (P=0.107).

Wilson et al.	T=15/15/14 C=19/16/15	Epidural: Ketamine	Epidural: bupivacaine 0.5% of 1 mg/kg with 0.5 mg/kg ketamine bolus before starting surgery.	Epidural bupivacaine 0.5% of 1 mg/kg with saline was given before starting surgery	Lower limb amputation	VAS, MPQ, NPS, HADS	3 months: Phantom pain in ketamine group 6/15 (40%) and control group 7/19 (37%)(P=0.867). Stump pain ketamine group 5/15 (33%) and saline group 9/19 (43%) (P=0.635). 6 months: Phantom pain ketamine 6/15 (40%) and saline 3/16 (19%) (P=0.252). Stump pain ketamine 7/15 (43%) and saline group 5/16 (32%) (P=0.609). 12 months: Phantom pain ketamine group 7/14 (50%) and saline 6/15 (50%) (P=0.867). Stump pain ketamine 3/14 (21%) and saline 5/15 (33%) (P=0.682). Median NPS score decreased at all times postoperatively in both groups.	Anxiety significantly decreased in ketamine group compared with the preoperative value till year one (P< 0.001) whereas there was no difference b/n the preoperative and postoperative anxiety value till year one in saline group (P=0.071). Depression level remarkably reduced in ketamine group at 3, 6 and 12 months compared to placebo group (P=0.003).

Katz et al.	T=36 C=36/38	Ketamine	Group 1: Fentanyl=1 µgm/kg IV bolus and 25 µgm/kg/hr infusion 5 minutes before induction of anaesthesia Ketamine: 0.2 mg/kg IV bolus, followed by 2.5 µgm/kg/hr infusion 10 minutes before skin incision.	Groups 2 and 3: IV fentanyl and saline (bolus plus infusion) before incision (equivalent amount with group 1)	Radical prostatectomy	MPQ,VAS, FUPQ	6 months: Most intense pain after surgery (VRS: mean ±SD): G1 (5.1 ± 1.9), G2 (5.6 ± 2.2) and G3 (5.1 ± 2.5). VAS-rest pain G1 (2.3 ± 1.2), G2 (2.8 ± 1.1) and G3 (3.4 ± 3.0) respectively.	-
Nikolajsen et al.	T=17/16/12 C=20/20/16	Epidural (morphine and bupivacaine)	Epidural: 0.2 mg morphine and bupivacaine 0.5% of 5-10 ml bolus were given 18 hr before amputation and continued till end of surgery	Epidural: saline and morphine 5-20 mg orally or intramuscularly six times daily before surgery	Lower-limb amputation	VAS	Phantom pain 3 months: block 14/17 (82%) *vs.* control 10/20 (50%) (P=0.09). 6 months: block 13/16 (81*%) vs.* control 11/20 (55%) (P=0.2). 12 months: block 9/12 (75*%) vs.* control 11/16 (69%) (P=1.0).	Phantom pain: 3 months: Block *vs.* control (82% *vs.* 50%) 6 months: Block *vs.* control (81% *vs.* 55%) 12 months: Block *vs.* control (75% *vs* 69%)
Dualé et al.	T=34 C=35	Ketamine	B=1 mg/kg IV before surgery, INF=1 mg/kg/hr during surgery and 1 mg/kg/24 IV	Saline during induction, operation and for 24 hrs	Thoracotomy	VAS	4 months: Ongoing pain (NPSI)=ketamine 8 (23.5%) *vs.* placebo 12	4 months: Ongoing pain (PNSI) (mean ± SD): ketamine group 8

			after surgery				(34.3%) (P=0.325).	(23.5) and placebo group 12 (34.3) (P=0.325). Evoked pain (NPSI)=ketamine 13 (38.2%) *vs.* placebo 16 (45.7%) (P=0.529). Neuropathic pain score (>0): ketamine 16 (47.1%) *vs.* placebo 24 (68.6%) (P=0.070).
Joseph et al.	T=16 C=19	Ketamine	B=0.5 mg/kg at induction INF=3 µgm/kg/min during operation and 1.5 µgm/kg/min for 48 h after operation	IV placebo (a saline solution under the same infusion modalities).	Thoracotomy	NRS	3 months: NRS at rest (mean ± SD): ketamine group: 1.1 ± 2.1 and control group: 0.3 ± 0.7 (P=0.385).	3 months: NRS during abduction (mean ± SD): ketamine group: 1.3 ± 2.3 and control group: 1.1 ± 2.5 (P=0.589).
Can et al.	T=20 C=20/20	Epidural	Pre-group: 10–15 mL of 0.1% levobupivacaine epidural was given before anaesthesia. Post incision group: remifentanil 0.25–0.50 g/kg/hr infusion started 10 minutes after incision	Control group: no epidural analgesia received before and during operation	Thoracotomy	VAS	3 months: VAS score (≥ 3): control 4 (20%), post-incision group 4 (20%) and pre-group 3 (15%) (P=0.896). 6 months: VAS score (≥ 3): control 6	3 months: VAS score (mean ± SD): Control group (1.90 ± 0.96), Group post-incision (1.80 ± 1.00) and Pre-emptive group (1.65 ±

							(30%), post-incision group 5 (25%) and pre-group 4 (20%) (P=0.769)	0.87) (P=0.664). 6 months: VAS score (mean ± SD): control group (2.10 ± 0.96), Group post-incision (1.95 ± 0.99) and Pre-emptive group (1.70 ± 0.92) (P=0.348).
Ryu et al.	T=65 C=68	Ketamine added to epidural	G1: 100 mg ketamine and 2 µg/mL fentanyl were given in combination epidural levobupivacaine before surgery	G2: 2 µg/mL of fentanyl was given in combination with epidural levobupivacaine before surgery	Thoracotomy	VAS	3 months: Pain at rest ketamine group 33/65 (51%) and control group 29/68 (43%) (P=0.348).	3 months: pain with movement (coughing) ketamine group 44/65 (68%) and control group 50/68 (74%)(P=0.46).
Hayes et al.	T=15 C=17	Ketamine	Ketamine group: 0.5 mg/kg IV bolus before anaesthesia, followed by 0.15 mg/kg/hr for 72 hrs after operation	Control group: placebo preoperatively, followed by saline infusion for 72 hrs after operation	Below knee amputation		6 months: phantom pain ketamine group 7 (47%) *vs.* control 7 (71%) (P=0.28) and stump pain ketamine group 7 (47%) *vs.* control 6 (35%) (P=0.72).	

Table S1: Summary characteristics of review studies.