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Review article

Supraclavicular Brachial Plexus Block by Ketamine-Bupivacaine in Comparison to Bupivacaine with Intravenous Ketamine Infusion

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ABSTRACT

Objective: The aim of this review was to compare Supraclavicular Brachial Plexus Block by Ketamine-Bupivacaine versus Bupivacaine with Intravenous Ketamine Infusion **Methods:** A comprehensive search was conducted in search engines from August 2000 to July 2021, using the keywords . The reviewers evaluated relevant literature references as well. Only the most recent or complete study was taken into account. **Results:** The reviewed literature showed that VAS was significantly lower at 12 h in group 1 but insignificantly different at 1/2, 1, 1.5, 2, 3, 4, 6 and 24 h between both groups; so do postoperative heart rate and mean arterial pressure. Onset of sensory block and onset of motor block was significantly lower in group 1. Duration of sensory block and duration of motor block was significantly higher in group1. Both time of 1st rescue analgesia was significantly delayed in group 1 and total ketorolac requirements were significantly lower in group 1. Sedation score was significantly different between both groups. On the opposite postoperative respiratory rate and SpO2 were insignificantly different between both groups. **Conclusion:** Using ketamine bupivacaine in supraclavicular brachial plexus block in upper limb surgeries is effective in enhancing onset of the brachial plexus block and prolonging the duration of the brachial plexus block with no hemodynamic changes, it effectively prolongs postoperative analgesia and lowers the analgesic requirements compared to intravenous ketamine infusion.

Introduction:

The ventral rami of the (C5-C8) and (T1) spinal nerves are joined to form the brachial plexus (BP), a network of nerves. Three cords (medial, lateral, and posterior), six divisions (three anterior and three posterior), three trunks (superior, middle, and inferior), and five terminal branches result from their union (axillary, musculocutaneous, radial, median and ulnar nerves)[1].

The long thoracic nerve, which innervates the serratus anterior muscle, the dorsal scapular nerve, which innervates both the levator scapulae and the rhomboid muscles, and a branch of the phrenic nerve, which innervates the diaphragm, are just a few of the nerve branches that emerge from the roots of the BP. The suprascapular innervates the supra- and infraspinatus muscles as well as the subclavius muscle from the trunks of the BP)[2].

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The entire arm receives simultaneous motor and sensory supply from all of the terminal branches of the BP [3]. Often, an interscalene, supraclavicular, infraclavicular, or axillary route is used to provide brachial plexus blocks. The "spinal of the arm" or supraclavicular level is optimal for providing an anaesthetic block for surgery or intra- and postoperative pain control for the entire upper limb because it produces a quick and high-quality block with the best success rate [4]. It offers analgesia to the upper extremities for post-surgical and traumatic pain, complex regional pain syndrome, post-amputation pain, vascular disorders, and tumor-related pain, as well as general surgery of the upper extremity for both adults and children. Prior to its use, relative and absolute contraindications must be taken into account and may include severe coagulopathies, pre-existing neuropathies, or nerve damage [5].

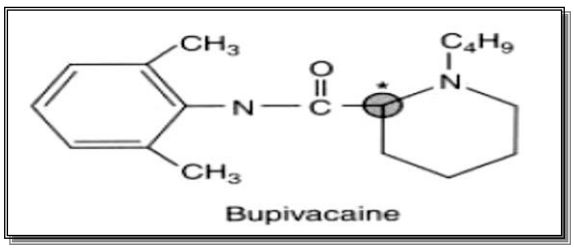
Contraindications

For fear of diaphragmatic paresis and pneumothorax events, the patient may refuse the procedure, have an allergy to local anaesthetics, have an infection at the injection site, have cancer at the needle entry site, have coagulopathy, or if there are any preexisting neural deficits in the block's distribution[6].

Complications

Pneumothorax (incidence: 1-6%), injury to the recurrent laryngeal nerve causing hoarseness of voice (incidence: 1%), injury to the phrenic nerve causing hemi-diaphragmatic paresis (33%), and vascular puncture (incidence: 0.4%)[7]. With a reported incidence of 1%, Horner's syndrome (miosis, ptosis, and anhidrosis) is the result of the ipsilateral sympathetic cervical chain being paralysed by medication, surgery, or local compression [8]. Risk for infection, bleeding, and neuropathy [9]. Bupivacaine (Marcaine©) is 1-butyl-N-(2, 6-dimethylphenyl) piperidine-2-carboxamid [10].

Figure 1: Bupivacaine [10]



Its molecular weight is 288 with pKa 8.1and the partition coefficient is 346. The protein binding 95% and the dose is 2mg /kg increased to 3mg/kg with vasoconstrictor. It possess high potency and long duration of action [11]. Clinical uses including infiltration (0.25%), peripheral nerve blocks (0.375–0.5%), spinal (0.5 and 0.75%), and epidural (0.5 and 0.75%) anesthesia. It is not used for IV regional anesthesia [12].

Concentrations vary from 0.05% (epidural continuous infusions for labor analgesia and acute pain management) to 0.5% (spinal anesthesia and peripheral nerve blocks) [12]. It's bio transformed in the liver followed by renal excretion [13].

Excitation or depression, shivering, muscle twitching, and tremors are some of its negative side effects, which are initially felt in tiny muscle groups (e.g. face and extremities). They are gradually replaced by more widespread convulsive activity. Effects that inhibit, such coma and apnea [14]. High plasma levels and the associated myocardial depression, decreased cardiac output, heart block, hypotension, bradycardia, ventricular arrhythmias, including ventricular tachycardia and ventricular fibrillation, and cardiac arrest can result from high doses or unintentional intravascular injection [14].

Urticaria, pruritus, erythema, laryngeal edoema, angioneurotic edoema, tachycardia, wheezing, nausea, vomiting, dizziness, syncope, increased sweating, raised fever, and perhaps anaphylactoid-like symptoms (including severe hypotension) [15].

Lagan and McLure, 2004 [16] indicated that careful technique, needle positioning, aspiration before to injection, slow injection, delivering test dosage, understanding of the maximum dose, and use of adjuvant can guard against toxicity (opioid, clonidine, bicarbonate). Smith, 2007[14] Early reassurance, preservation of oxygenation, and avoidance of acidosis were noted as treatments. Thiopental, 2-3 mg/kg, or Midazolam, 0.03-0.06 mg/kg, which is similar but takes a little longer to work, or Propofol anticonvulsant, which is immediately available with no delay for mixing, should be used to cease convulsant neuronal activity. 20% lipid emulsion is first given for provoked cardiac arrest as a 1.5 mL/kg/min bolus, then as a continuous 0.25 mL/kg/min infusion, one to two further boluses may be given until 10 min after restoring hemodynamic stability, with a maximum of 10 mL/kg in 30 min, and monitoring

for 12 h after [17]. Abdallah.et.al.,2016 [18], claimed that the following ultrasound images of different tissues are used for regional anesthesia:

Table 1: Ultrasound image of various tissues for regional anesthesia [18].

Tissue	Ultrasound image for regional anesthesia
Arteries	Anechoic/hypoechoic, pulsatile, non-compressible
Veins	Anechoic/hypoechoic, non-pulsatile, compressible
Fat	Hypoechoic, compressible
Muscles	Heterogeneous (hyperechoic lines within a hypoechoic tissue background)
Tendons/ fascia	Hyperechoic
Bone	Very hyperechoic with acoustic shadowing behind
Nerves	Hyperechoic below the clavicle/ hypoechoic above the clavicle
Air bubbles	Hyperechoic
Pleura	Hyperechoic line

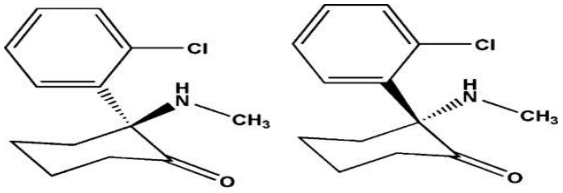
Anesthesiologists can more precisely administer regional anaesthetic thanks to ultrasound-guided peripheral nerve blockade, which also expands their capacity to block smaller nerves and those in more challenging anatomical placements. Its benefits include direct observation of the nerves and the structures around them (such as the arteries), reducing problems (such as accidental intraneural or intravascular injection), and direct observation of local anaesthetic dissemination. The longer block duration and quicker onset are caused by the more precise deposition, which also improves block quality and lowers the dosage of local anaesthetics [19].

Sonography Confirming Local Anesthetic Spread:

When injecting through a needle, look for a dark (anechoic) mass of local anaesthetic distribution [20]. Ponde et al., 2015 [21], clarify the nerve border; separate the connected structures[22].

Color Doppler will help to visualize the flow of local anesthetic out of the catheter and help to confirm the tip location [20]. The only anaesthetic on the market with analgesic, hypnotic, and amnesic properties is ketamine. Due to the electrical dissociation between the limbic and cortical circuits, it causes a state of dissociative anaesthesia. It is a highly helpful medicine when used properly [23].

Figure 2: The optical isomers of ketamine [24]



R-(–)- ketamine *S*-(+)- ketamine

The molecular weight of the ketamine molecule, 2-(O-chlorophenyl)-2-methylamino cyclohexanone, is 238. The racemic combination has a pKa of 7.5, is easily water soluble, and is made in a mildly acidic solution (pH 3.5-5.5). Two optical isomers make up a chiral centre (enantiomers). Ketamine crosses the blood-brain barrier more quickly than thiopental and has a high lipid solubility (5–10 times that of thiopental). The cyclohexanone ring is demethylated and hydroxylated in the liver. Conjugated metabolites are eliminated in urine. Nor ketamine has 20–30% of the parent compound's action and an adult elimination half-life of 2–3 hours [24].

Table 2: Pharmacokinetics of ketamine [24]

Onset of action (I.V)	30 s
Bioavailability -I.M -Intranasal -Oral	 93% 25–50% 20–25%
Protein binding	20–50%
Distribution half life	10 min
Elimination half life	2–3 h
Site of metabolism	Liver: cytochrome P450
Metabolites	Norketamine, dehydronorketamine

Ketamine's effects on the central nervous system (CNS) are principally due to noncompetitive antagonistic interactions at the Ca2+ channel pore of the N-methyl-D-aspartate (NMDA) receptor. It lessens glutamate's presynaptic release. Naloxone does not counteract the analgesic effects of ketamine because the S (+) enantiomer interacts with opioid receptors with a predilection for mu and kappa receptors and has an affinity for NMDA receptors that is 3- 4 folds stronger for the S (+) form than the R (-). Moreover, ketamine inhibits neuronal sodium channels, which results in anticholinergic symptoms (such as tachycardia and bronchodilation) and has an antagonistic interaction with monoaminergic, muscarinic, and nicotinic receptors [24].

Table 3: Doses &Uses of ketamine [25]

Induction of general anesthesia	0.5-2 mg/kg IV4-6 mg/kg IM
Maintenance of general anesthesia	0.5-1 mg/kg IV with N_2O 50% in $O_2$15-45 µg/kg/min IV with N_2O 50-70% in O_2 30-90 µg/kg/min IV without N_2O
Sedation and analgesia	0.2-0.8 mg/kg IV over 2-3 min 2-4 mg/kg IM
Preemptive/preventive analgesia	0.15-0.25 mg/kg IV
Regional analgesia & anesthesia	0.25- 1 mg / kg

CNS effects

The so-called "dissociative" anaesthetic state that is brought on by ketamine has been defined as a functional and electrophysiological separation of the limbic and thalamo-neocortical circuits. The alpha rhythm is absent, and theta activity is prevalent in the EEG. The distinctive clinical state caused by ketamine is often a catalepsy in which the corneal and light responses are unaffected and the eyes remain open with a sluggish nystagmic stare. In the context of sufficient surgical anaesthetic, varying degrees of hypertonus and occasionally deliberate movements unrelated to painful stimuli are observed. Without any clinical indication of seizure activity, studies have shown that ketamine treatment causes excitatory activity in the thalamus and limbic circuits. As a result, ketamine wouldn't likely cause convulsions in patients with seizure disorders, and experimental studies actually seem to show that ketamine possesses anticonvulsive and possibly even neuroprotective characteristics [26].

Compared to when consciousness is lost, analgesia happens at blood concentrations that are much lower. Both the racemic combination and S-(+)-ketamine fit this description. Ketamine raises intracranial pressure, cerebral blood flow (CBF), and cerebral metabolism (ICP). We don't yet know how S-(+) -ketamine affects ICP. Although racemic ketamine's effect on cerebral autoregulation has not yet been investigated, S-(+)-ketamine has no impact on it. Common symptoms include pupillary dilation, nystagmus, salivation, and lachrymation [26].

Emergence reactions

With ketamine emergence, psychic feelings include changes in mood and self-perception, floating sensations, vivid dreams or illusions, and occasionally open delirium. Upon complete awakening, these dreams and illusions typically vanish. Therefore, it's crucial to go over these ketamine side effects with patients. The prevalence of psychic consequences is between 5% and 30%. Increased ages, female gender, patients who typically dream, quick intravenous administration, and high doses are all linked to higher incidence. It has been noted that ketamine causes schizophrenia patients to experience psychoses. However, it has not been connected to persons without recognised psychiatric disorders experiencing persistent psychotic symptoms. Midazolam (0.07-0.1 mg/kg), diazepam (0.15-0.3 mg/kg), and lorazepam (2-4 mg) I.V. have been demonstrated to be useful in reducing psychological reactions. Moreover, the occurrence is reduced when combined with other sedatives, hypnotics, and general anaesthetics [24].

Cardiovascular effects

The cardiovascular effects of ketamine are particularly diverse. When it is administered, tachycardia, elevated blood pressure, and increased cardiac output are frequently observed. It is yet unknown what exactly causes this centrally controlled sympathetic response. Nonetheless, ketamine has a direct cardiac depressive effect when autonomic control is absent, which is typically overridden by this central reaction. Similar hemodynamic side effects are produced by identical dosages of S-(+)-ketamine. Giving ketamine as a continuous infusion and taking a benzodiazepine

can both lessen the unfavourable cardiovascular consequences [27].

Respiratory system

The airway is typically well maintained and some pharyngeal and laryngeal reflexes are preserved during ketamine anaesthesia. This is not a guarantee, though, and when necessary, traditional methods for preventing aspiration and maintaining a patent airway must be used. Laryngeal spasms have been known to occur more frequently when ketamine is used. As partial airway obstruction is a common ketamine side effect and typically responds to easy airway movements, many of these reports may be related to it. According to compiled statistics, laryngospasm caused by ketamine that was severe enough to warrant intubation only happened in 0.02 percent of instances, but it happened in 1.75 percent of procedures involving drugs other than ketamine [28]. Ketamine likely has two different mechanisms of action that cause bronchodilation: first, a central effect that causes catecholamine release and stimulates 2 adrenergic receptors, causing bronchodilation; and second, inhibition of vagal pathways that results in an anticholinergic effect that directly affects bronchial smooth muscle[29].

Gastro-intestinal tract

Ketamine causes increased salivation, which can block or cause laryngeal spasms in the airways. Atropine is often administered either as a premedication (10-20 g/kg) intravenously to a maximum dose of 0.5 mg 30 minutes prior to surgery or during induction (10-20 g/kg) intramuscularly to a maximum dose of 0.5 mg. As an alternative, glycopyrrolate (0.01/kg to 0.2 mg intravenously) may be utilised. The effects of ketamine on the gastro-intestinal tract may be advantageous when used for sedation in the Intensive Care Unit (ICU), as enteral feed is tolerated better with ketamine sedation than with opioids. Compared to thiopental or propofol, ketamine has a higher propensity to induce nausea and vomiting; however, because of its opioid-sparing properties throughout the perioperative period, the overall incidence of postoperative nausea and vomiting is decreased [30].

Skeletal muscle

Ketamine improves the tone of skeletal muscles. This becomes gradually less evident after the initial intravenous bolus. The administration of benzodiazepines may help. Although it is rarely a concern during surgery, it is sometimes necessary to relax with benzodiazepines or even muscle relaxants in muscular young men, especially those who need to manipulate fractures [31].

Eyes

Ketamine induction causes a little increase in intraocular pressure, which is maintained for another 15 minutes. This elevation was not shown to be clinically significant in human investigations, and it was also smaller than that brought on by laryngoscopy. The extra-ocular muscles' greater tone, increased blood flow from the increased cardiac output, and an increase in arterial paco2 caused by ketamine are thought to be the cause of this spike. These side effects are lessened by balanced anaesthesia and regulated breathing, which also lessens the nystagmus that is typically associated with ketamine anaesthesia. Hence, using ketamine for intraocular surgeries is safe. Ketamine is still best avoided in cases of open eyes or glaucoma in favour of medications that don't raise intraocular pressure and can lessen the reaction to intubation [31].

Placenta

The placenta is crossed by ketamine. Hence, newborn newborns after a Caesarean section under ketamine anaesthesia will only be partially asleep, and they should be treated as such [32].

Thyroid

In patients who are hyperthyroid or on thyroxin, ketamine has been known to cause hypertension and supraventricular tachycardia. Thus, it is advised against using ketamine in these people [32]

Metabolic

Ketamine causes a rise in porphyria markers in the serum but no changes in the patient's clinical condition.

Potential Adverse Effects [33]:

Illusion and hallucination, Agitation during recovery Misaligned airways needing head repositioning (occasional), temporary laryngospasm, temporary respiratory depression or apnea, Hypersalivation, Emesis, hypertonicity of the muscles and careless, erratic motions (common), Short-lived non-allergic rash on the face and neck, clonus, or hiccups.

Postoperative pain:

Acute postoperative pain is a common side effect of surgery that can delay healing and discharge as well as increasing the risk of wound infection and cardiovascular and respiratory problems.

Acute pain that is not treated results in decreased patient satisfaction, increased morbidity and death, as well as financial strain on the patient and the healthcare system. Chronic postsurgical pain is the term for acute pain that continues after surgery but cannot be controlled (CPSP) [34].

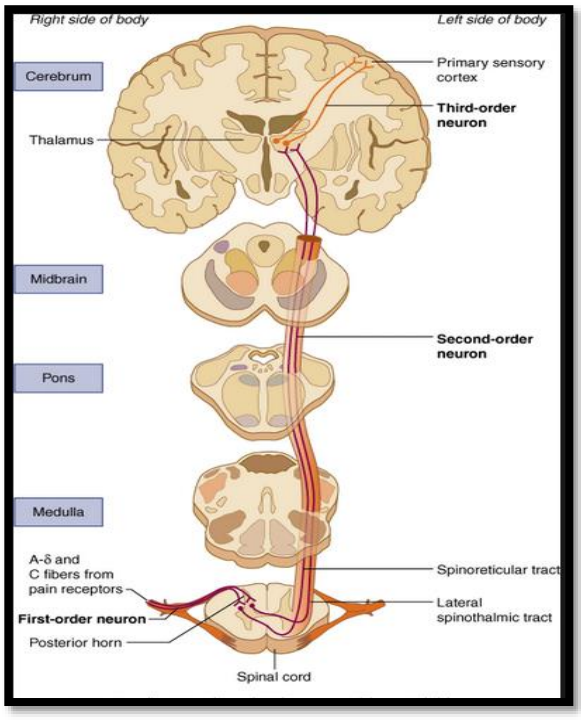
Immediate postsurgical pain is nociceptive or neuropathic and results from inflammation brought on by tissue trauma or direct nerve injury. Local inflammatory mediators are released by tissue trauma, and these mediators can cause hyperalgesia (increased sensitivity to stimuli in the vicinity of an injury) or allodynia (misperception of pain to nonnoxious stimuli). Sensitization of peripheral pain receptors (primary hyperalgesia) and increased excitability of central nervous system neurons are additional factors causing both hyperalgesia and allodynia (secondary hyperalgesia) [35].

Genetic variables should be taken into account in the context of the interrelated physiologic, psychological, and environmental elements that affect how the body reacts to pain and analgesia, it is becoming increasingly clear. The need for postoperative opioids varies greatly between patients due to genetic variables affecting opioid pharmacodynamics and pharmacokinetics (metabolising enzymes, transporters, and receptors). Examples in particular include genetic polymorphisms, which alter plasma levels of methadone and the active metabolites of codeine and tramadol. Opioid analgesia has historically been utilised to treat pain in order to target the central mechanisms responsible for pain perception. Many medications are used in a multimodal approach that recognises the pathophysiology of surgical pain in order to reduce pain receptor activation and the local hormonal response to injury [36].

This strategy reduces a medication's and a mechanism's dependence. For instance, anti-inflammatory drugs can reduce the hormonal response to injury, local anaesthetics can block the activity of pain receptors directly, and medications like acetaminophen, ketamine, clonidine, dexmedetomidine, gabapentin, and pregabalin can block the release of certain neurotransmitters to reduce pain. Table 10 lists the non-opioid medications used to treat postoperative pain [35].

The dorsal horn of the spinal cord is where the integration of peripheral nociceptive and descending modulatory input (i.e. serotonin, norepinephrine, -amino butyric acid, and encephalin) takes place. Painful stimuli are transduced by peripheral nociceptors and transmitted by A-delta and C nerve fibres from peripheral visceral and somatic sites. Complex spinal cord modifying factors control how nociceptive information is transmitted in the future. Certain impulses travel to the ventral and ventrolateral horns to start segmental (spinal) reflex reactions, which can result in altered gastrointestinal motility, decreased skeletal muscle tone, and suppression of phrenic nerve function. Others are sent through the spinothalamic and spinoreticular fibres to higher areas, where they cause suprasegmental and cortical reactions that ultimately result in the feeling of and affective component of pain [37].

Figure 3: Pain pathway [37]



Pain assessment:

To give the best post-operative pain care, pain assessment and reassessment are necessary. In order to determine whether pain management is adequate, whether analgesic or analgesic dose adjustments are necessary, whether changes to the post-operative pain management plan or additional interventions

are warranted, and whether specialty consultation or other measures are required in the case of difficult to manage pain, pain assessment is helpful. Patient self-report is the main source of all pain assessments due to the fact that pain is fundamentally subjective. Clinicians shouldn't rely entirely on "objective" measurements to assess the existence or severity of pain because they are neither valid nor trustworthy. Examples of such measures are pain-related behaviors and vital signs. Even at similar pain levels, people may behave very differently in terms of pain. Hence, it is crucial to evaluate behavioral observations carefully, even though assessments of pain behaviors may enhance information from self-reported pain [38].

Validated pain assessment tools use different methods to measure pain, including visual analogue scales, numeric or verbal rating scales, symbols and others. The panel recommends that clinicians use a validated pain assessment tool, although there is inadequate evidence on the effects of different pain assessment tools on post-operative pain outcomes to guide recommendations on which specific tools to use. Therefore, the selection of a particular pain assessment tool should be on the basis of factors such as developmental status, cognitive status, level of consciousness, educational level, as well as cultural and language differences [38].

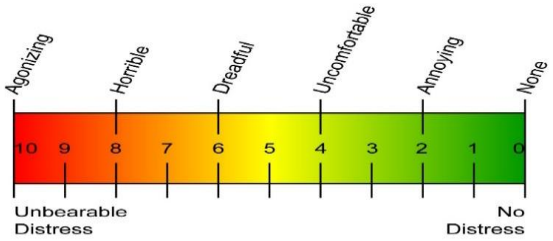
Numeric Rating Scale (NRS for pain) for pain:

In the clinical setting, the NRS for pain is simple to use and is one of the most common approaches for quantifying pain. Patients rate their level of pain on a scale from 0 to 10, where 0 represents no pain and 10 represents the worst possible pain. An effective method for elucidating the connection between pain and activity is the NRS for pain [39].

Visual Analog Scale (VAS):

Similar in concept to NRS for pain, the VAS is another established method of measuring pain. The VAS consists of a 10-cm line with one end labeled “no pain” and the other end labeled “worst pain imaginable.” The spot on the line where the patient feels the most discomfort is marked. The line's distance from the patient's mark is measured in millimeters and noted. The key theoretical benefit of the VAS is that it allows for a more thorough rating of pain as illustrated in since it does not restrict pain to defined levels of severity [40].

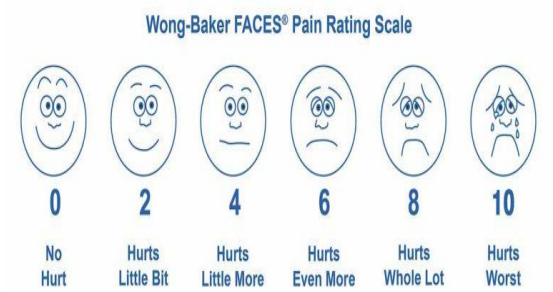
Figure 4: Visual analogue scale [40]



Faces pain scale:

This scale displays images of various face expressions that represent a variety of emotions. This scale may be helpful for patients with mild to moderate cognitive impairment, young children, patients with other linguistic challenges, and patients.

Figure 5: Faces pain scale [41]



McGill pain questionnaire (MPQ):

Twenty groups of seventy-eight pain adjectives were further divided into sets of words expressing the sensory characteristics of pain [42].

Assessment of chronic pain

The classification of chronic pain problems depends critically on an accurate assessment of pain. Table summarises methods for evaluating various chronic pain domains [43].

Table 4: Approaches for assessing different domains of chronic pain [43]

Pain Domain	Measures
Sensory and Affective Qualities of Pain	
Pain Intensity-The strength or "loudness" of the pain	Categorical Scales; Numerical Rating Scales (NRS for pain); Visual Analog Scales (VAS); Faces Scale; Verbal Descriptor Scales; Brief Pain Inventory; Graded Chronic Pain Scale
Pain Affect-How unpleasant of disturbing the pain feels	Categorical Scales; Numerical Rating Scales (NRS for pain); Visual Analog Scales (VAS); Faces Scale; Verbal Descriptor Scales
Perceptual Qualities of Pain-Description of sensory and other features of the pain, how the pain feels	McGill Pain Questionnaire (MPQ); PainDetect; Neuropathic Pain Scale; Neuropathic Pain Symptom Inventory; Leeds Assessment of Neuropathic Symptoms & Signs (LANSS); Dolour Neuropathique-4 Questions (DN4)
Temporal Characteristics of Pain	
Pain Duration-Time since onset of chronic pain in months or years	Retrospective self-report
Pain Variability-The presence vs. absence of pain and fluctuations in pain intensity over time.	Patient report of the percentage of the waking day during which pain is present; Ecological Momentary Assessment (EMA)
Modifying Factors-Factors that exacerbate or ameliorate the pain	Retrospective self-report; EMA
Other Pain Features	
Pain Location(s)-areas of the body in which patient experiences pain; bodily extent of pain	Pain Drawing (Paper-and-Pencil or Electronic)
Provocative Pain Measures-Measures collected via physical exam in order to provide diagnostic information	Straight Leg Raising; Digital Palpation
Pain Behaviors-Overt behaviors that convey to the observer that the individual is experiencing pain	Facial Expressions; Limping, Guarding, Bracing, etc…

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