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Session: Ketamine: What is old is new again

Presenter: Sanjog Pangarker, MD

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Dr. Robin Masheb: Good morning everyone, and welcome to Spotlight on Pain Management. This is Dr. Robin Masheb, Director of Education at the Prime Center, and I will be hosting our monthly pain call entitled Spotlight on Pain Management. Today’s session is Ketamine: What is old is new again. I would like to introduce our presenter for today, Dr. Sanjog Pangarker. Dr. Pangarker completed residencies in internal medicine and physical medicine and rehabilitation at Johns Hopkins and fellowship in pain medicine at UCLA. Dr. Pangarker is currently the director of inpatient and interventional pain services. He is associate professor of medicine at UCLA and teaching faculty for the physical medicine and rehabilitation residency and pain fellowship programs housed at UCLA and the VA. His research interest is in ketamine, which he will be talking about today. We will be holding questions for the end of the talk. If anyone is interested in downloading the slides from today, please go to the reminder email you received this morning and you will be able to find the link to the presentation. Immediately following today’s session, you will receive a very brief feedback form. Please complete this as it is critically important to help us provide you with great programming. And now I’m going to turn this over to our presenter, Dr. Pangarkar.

Dr. Sanjog Pangarker: Thanks Robin. Thanks Heidi. Hello and good morning everyone. I hope everyone is having a good New Year, so happy New Year. I’m just going to go ahead and jump into ketamine and the topic that we have some time to talk about. I have only close to 30 slides, so it should leave enough time for discussion at the end. I’d really like to hear what folks are out there doing with ketamine because we do know that a lot of facilities within the VA use ketamine, but we haven’t been able to consolidate exactly which facility is using it and how much and how frequently. So that would be really nice to get an idea of what’s being done outside. So I’ll go ahead and get started. I have no disclosures to discuss.

The outline of today’s lecture will be essentially talking about a case report. And why that case report is important to me, specifically, is because much of medicine has moved to this concept of evidence base and I think that’s appropriate, obviously. But medicine can also be very anecdotal, and when you see something successfully occur for a patient that changes their life, you start to look into it a little further. And that’s essentially what happened here at West L.A. where we starting having some success with this treatment and decided that we would invest essentially in it and the staffing and the manpower to keep this going. But we’ll discuss that a little bit more as well as other cases we’ve done, the different types of cases we’ve used before. I’ll talk a little about the history of the drug, some of the pharmacology and indications, contraindications, precautions we take here at West L.A. and probably most facilities take, and evidence behind its use, and hopefully again, we should have some time for questions so it shouldn’t be a problem.

I’m going to go ahead and start with this case. This is a gentleman who I was involved with. He’s a 50-year-old right-handed Veteran who presented with right-sided knee pain. He was involved in the Persian Gulf War and was injured during that time. He had daily symptoms of moderate pain in his right knee. His diagnosis was moderate-to-severe knee arthritis, and essentially he was tried on most conventional treatments for his pain. So he had the typical things that we do for people with arthritis is anti-inflammatories, physical therapy, bracing, topical analgesics. He also had steroid injections and a number of other [unintelligible 4:07] supplements tried. None of those offered him significant benefit, and eventually he ended up seeing orthopedic surgery and had arthroscopy performed. He had essentially two arthroscopies performed, and after the second, he started developing significant allodynia in his right lower extremity.

So for those who don’t know, and I think most people do know what allodynia is, but allodynia is essentially pain that is out of proportion to stimulus. So if you step on a thumbtack, obviously that would hurt and it should hurt. But if the wind from the door opening brushes up against the knee and causes severe pain, that really shouldn’t bother somebody. So that’s really allodynia 101. In any case, so this is of course when he was around 32, 33 years old. But he started developing skin crusting, a discoloration from the knee extending down to the toes. He essentially was diagnosed with complex regional pain syndrome type 1 and over the next 17 years underwent typical treatments that we would render for somebody in a VA pain clinic. It is a multi-disciplinary pain clinic and we do have quite a bit of capacity, so he got everything you would typically think of, and that’s from interventional procedures like sympathetic nerve block, even spinal blocks which he had pretty regularly for cleaning of his leg by podiatry and plastics. But he also had things like spinal cord stimulator trials. He had behavioral health with psychological counseling for quite some time. He had a number of medications, tried all of the neuropathic agents that were available commercially were used in some capacity for him. And eventually he ended up being placed on opiates.

So he ended up being on close to 400 mg of morphine equivalent, and that’s through a number of different types of meds used. We triedfentanyl, we tried methadone, Levorphanol, things that we thought would have an NMDA effect, and so we tried the conventional medications as well as the antidepressants that were available including SNRIs for him. None of those really offered him significant benefit and he was living fairly uncomfortably. The other thing I should point out is his right knee was stuck in extension. So the problem with that is that is if his right knee is in extension and it’s slightly shortened, which it was, he really couldn’t ambulate at a household level or at a community level. He could get around his house minimally, but he was essentially rendered stuck in a wheelchair and that’s how his problems really began.

So his pain and disability or debility lead to him becoming obese, developing muscle atrophy, developing osteoporosis. He ended up having two significant falls where he fell out of his wheelchair, and in the first one, he fractured his distal tibia and the second one he fractured his hip. So over time he ended up developing contractures of his lower extremities, this chronic cellulitis, which required spinal blocks to clean. So we’d bring him in, our anesthesia service would actually perform a spinal, he’d be brought to the recovery area where podiatry and plastic surgery would debride the leg. And you can see from the previous picture here that that’s a fairly abnormal looking knee, or leg sorry, but that’s actually after cleaning. And that’s about as good as it would look. Most of the time it would look like it had fungus growing on it and be discolored greenish yellow.

It was pretty repulsive and difficult to look at for a lot of folks, and essentially he became isolated because of that, meaning if they decided to go to the mall as a family, he has children and a wife, his wife is now a nurse, they would actually go and people would just stare at his leg. And so by the time this happened enough, he decided he just didn’t want to leave the house anymore. Plus he couldn’t cover his leg when he was going anywhere because the tactile sensation from the cover would cause enough pain that he really couldn’t tolerate that. So he became more and more depressed, and with that he attempted suicide. Obviously we stepped in and had been present the whole time, but with that, we thought that the opiates were probably something that needed to be tapered. And how would we effectively do that for this gentlemen? What could we offer him as an adjuvant to allow for that taper to even occur?

And so we started thinking about ketamine for this gentleman to reduce both his neuropathic pain. If we got any anti-depression effects out of it, that would be wonderful, but really our goal was to see whether we could hit that NMDA receptor, reduce his pain overall, and allow him to get on with his life. And so we worked, we did a number of infusions of ketamine here at the, in our CPC, and we essentially stuck with about 80 mg per hour for four hours of ketamine. We did about 10 sessions over the course of a year, and with that, we were able to reduce his total morphine dose to 28 mg. Now if you think about this, the conflict of reducing somebody’s opiates for safety is something that’s talked about routinely now that we’re in this year with this opiate epidemic or opiate crisis. You hear this all the time. If a person is addicted or may be addicted or may be using too high of doses, we need to get them off. And obviously taking somebody off of medications they’ve been stable on for quite some time, or dependent on for quite some time, is difficult to do because the patient thinks that if, rightfully so, if my pain is poorly controlled now, what’s my pain going to be like when you take all my medications away?

And so during this whole time, we actually had him seeing our psychologist to make sure that there were no further suicide attempts or any other difficulties in that regard. So we were very vigilant about that. We ended up meeting with our orthopedic service several times, and I’m not sure, everyone works in the VA, you know how difficult it is to get funding to have food and that kind of thing available for meetings. So we actually sprung for the food ourself because we thought if we invite orthopedic surgery and we don’t have anything, they won’t show up, but they were kind enough to show up twice. The first time when we asked if we could have his right lower extremity removed, meaning an amputation, they just flatly refused and said no, we’re not going to do that. His complex regional pain syndrome will get worse and then we’ll be blamed for that problem.

And so we thought, well, look, if we can show and demonstrate to them that we can use ketamine in a way such that we can keep his pain well controlled, that his complex regional pain syndrome, or CRPS, wouldn’t spread, that we could actually allow them to do the amputation successfully. And with the amputation, if we could control the CRPS, we can make, we could get him into a prosthesis and hopefully allow him to be a community ambulator or at least get out of the house more frequently. With that, we thought his depression would improve. We thought that his life would be less isolated than it was.

And sure enough, so after this last dose of ketamine, or last infusion of ketamine, we ended up having him undergo an above-knee amputation with orthopedics fully engaged and helping with his treatment. We did place a catheter in the wound afterward and maintain that catheter for about a week just to make sure we had local, a local anesthetic effect as well as doing the ketamines.

And in any case, this is him now and so I actually share this picture. I didn’t change his picture or cover his eyes. He actually is part of our teaching group at the university, and so he is, he signed a release to allow me to use his picture. He’s very invested in this treatment as well as getting on with his life. So he’s now a community ambulator. He actually completed the driver safety courses and I believe he’s driving, though I don’t know that for sure. I think his car was modified the last I checked, they were working on that.

He’s just on ibuprofen and acetaminophen. He is on some psychological medications or medications for his mental health, which are being managed. But I was reading his chart last night just to make sure nothing had changed, and he broke his toe, his second toe on his left foot when he was out apparently working, in digging something in the back yard, working on a fence or something. So he is clearly out and about living his life, and so I think that’s one of the things, the anecdotal cases where you see where somebody’s life completely turns around and you think, wow, okay, this has given this man his life back. We need to do this more often if appropriate.

So what is ketamine and why do we expect this to help other patients? It’s essentially an FDA approved drug for the induction and maintenance of anesthesia. It’s considered a dissociative anesthetic, which mean it’s a peculiar anesthetic that causes a marked sensory loss and analgesia as well as amnesia, but it’s not actually accompanied by a loss of consciousness. And if you think about how this first came out or why it was first thought to be important is if you think about the ability to give somebody medications without compromising their airway or their blood pressure, it can be profound in combat situations, in areas where there may be a natural disaster and the doctors or nurses or medical teams are rushed into that area to give people medical care, a drug like this could be very good so you can give somebody enough pain control and amnestic but still allow them to be awake and present.

We use it, obviously, off-label. We use it for chronic pain, and many providers are using it for mental health disorders now. But the drug itself is very similar in appearance molecularly to PCP. And in fact, the history of this drug is actually quite interesting. Parke-Davis came out with this drug in 1962. And it really was supposed to be a kinder, more gentle PCP. And so PCP had a lot of problems with it, but it did provide profound analgesia, and yet it caused also a whole host of problems. Well, ketamine hits the PCP receptor, and so it was actually good in that way. It has had its own issues, of course, but it was first introduced in 1962. So we’re talking about a drug that’s quite old but has found a lot of new purposes and use.

And so the first trial started in ’64. The patent was received in ’66. and around 1970, obviously we were involved in the Vietnam War, and so many Veterans were getting this used on them for pain care as well as analgesia in the combat scenario. Around 1971, sub-dissociative doses were trialed. So lower dosing of this medication was trialed to see if we could get better relief. And over the course of the next 20 years, really not much happened.

One of the issues was that ketamine caused pretty bad nightmares while patients were under anesthesia or pretty significant psychomimetic problems. And so it essentially fell out of favor, it wasn’t used that often. But with 1987 occurring and the discovery of the NDMA receptor and the idea that ketamine actually works on this receptor, we started to see an increase in the number of people researching this. And by 1990 and through the 90s, ketamine started getting used again for cancer pain. Obviously with cancer pain, you start to think, well, if it works for cancer maybe it works for other things and you can start to see that non-cancer pain becomes a common entry point into the world of outpatient care and that’s what we’ve essentially been doing. By 1999 it was labeled a Schedule III medication, and it’s still a Schedule III medication at this point.

The pharmacology of this is it’s a PCP derivative, right? So people call it a number of things like Special K and Kit-Kats, and you’ll hear a lot of street verbiage for this drug because it is a party drug used at, outside of the context of the hospital or the medical setting. The major metabolite for this drug is ketamine and, or sorry norketamine, but both ketamine and norketamine are therapeutic. They both actually inhibit NMDA, which is essentially the basis of their effect. There’s a lot of other parts of it that they I’ll cover, but essentially think of this as an NMDA inhibitor, probably the most potent NMDA inhibitor that we have. There’s two stereoisomers. There’s the S-type and the R-type. Pretty much we use, here at our VA we use a racemic mixture because it’s generic which has portions of S and R. I do think that the S-type is going to become more commercially available. I don’t know if it’s available in the U.S. yet, but it is marketed as something called Ketanest but I don’t think we have it yet. Somebody may know of the call if we have it or not. But it is four times more potent that the R-variant, and so it can be, it may be able to get to the same effect with lower dosing. And if that was possible, then it certainly would be interesting to see how low we can go on the dosing of this drug.

Now we can give this medication through every route possible. So we typically give it IV but certainly it’s up to you. It’s done not uncommonly in the palliative care arena so you can give it IM. So places like our emergency room, which has now been approved to use ketamine, they can use ketamine at usually .5, 0.15 to .3 mg per kg, and so they can give it as an IM medication for acute pain. But some facilities, I know that Minneapolis was using it in the oral form for some of their patients, but it can be delivered in any route that you can get it into the body. And so it’s fairly quick in terms of its ability to pass the blood/brain barrier, and so it gets peak plasma concentration within a minute. And you have generally a half-life of about two to three hours. It is fairly extensively metabolized by the liver, and so eventually you get less than about 30% of drug available to you if you’re going to use the oral route. Peak is in about 30 minutes and the main substrates are the 2B6 and 2C9 and 3A4 routes. That’s a little bit, and that maybe important, methadone is also considered 2B6, fentanyl is a 3A4. So it does use some of the same routes through the liver that other conventional medications do, at least in the opiate arena.

It's not really an opiate though, and we’ll talk about that a little bit. But it does work on opiate receptors but it’s not really an opiate in the truest sense. The issue is side effects and there are plenty of side effects that occur with this drug. With appropriate planning, you can block most of these and [unintelligible 20:20] the emergence, which we’ll talk about, is something that is blockable. Hypertension also is blockable. So prior to our infusions, we’ll give patients midazolam IV as well as clonidine orally, and that will help with both of those issues, [inaudible 20:42] emergence and hypertension. The rest of these are also manageable, but they do occur and usually not at the doses we’re using [unintelligible 20:50] that but they can occur. So emergence is something that occurs after use of ketamine or during use of ketamine. You’ll see an altered short-term memory, decreased ability to concentrate, decreased vigilance, some cognitive issues, possibly hallucinations and nightmares, as well as nausea and vomiting.

So this is the type of thing you see after giving this medication, but again, some of these issues can be controlled for. And when patients become nauseous, we tend to give them a little Zofran during the course of their infusion and they tend to do pretty well with that. The nightmares we have had where patients have had significant nightmares such that they couldn’t tolerate any future treatments. And so we've had one gentleman recently, about two months ago, opt out of any further treatments because of that.

So the mechanism of action is a non-competitive NMDA antagonist. It binds, as I mentioned, to the PCP receptor and it inhibits NMDA receptor-mediated responses basically in the spinal cord and thalamus, disconnecting the two, if you will, and allowing the brain to separate a little bit. I use the analogy for patients as most of my patients are men. I say if you’ve ever driven a stick shift or manual car, when you engage the clutch, it essentially disengages the engine from the transmission, and that’s what our hope is, is that we’re disengaging the brain from the spinal cord and the rest of the peripheral nervous system so that we can find some benefit for patients. And that analogy tends to work for a lot of patients I treat who are young Veterans.

It also inhibits wind-up. And by inhibiting wind-up, it probably inhibits sensitization or central sensitization. And so that’ one of our hopes, obviously, for patients who may be developing chronic pain or who already have chronic pain that’s neuropathic in origin. It binds to the subtypes 2A and 2D and with any of these, you can see an increase in, meaning with use of this drug, you’ll see increased arterial pressure, increased heart rate, increased cardiac output. And so with all of that, you still see that the airway is protected. You may see some increased secretions of course, but even that is manageable.

So here’s a quick cartoon from MAYO that demonstrates the location of where we think the effect is. We believe it works at the area of the dorsal horn as you can see. And that’s important because that’s the entry point of the peripheral nervous system into the central nervous system. And if you think about spinal cord stimulators or things of that nature, our leads are placed in that same vicinity, and our goal is to modulate that general region. So in the substantia gelatinosa or the rexed laminae-2, we’re trying to deliver a treatment whether it be anesthetics, opiates, SNRIs, or anything of that variety into that location, and ketamine is no different but it also works at the level of the brain, so we get this disconnect in two locations which I think is what’s beneficial.

The other mechanism, and there’s quite a few other mechanisms of how ketamine works, but as I mentioned earlier, it does potentiate the mu and the delta opiate receptor so it does have some opiate-like effects. But those are not the primary effects and certainly not the ones that we’re interested in. The increased dopamine and noradrenaline release is also, I think, an important component to the pain relief as well as the calcium channel blockade or modulation, which I think can be helpful.

So now to the studies and sort of the evidence for it, most of what I’ve seen in terms of use of ketamine is really for complex regional pain syndrome. And that tends to be probably the most common use that I’ve seen in the pain world. Though we are using it now for a lot of different things including things like central headaches, deafferentations, so folks who have had their extremities removed traumatically with brachial plexus lesions, they’ve also responded.

But Finch and company actually used topical ketamine for patients versus placebo, and what they noticed that there was a decrease in allodynia locally in a symptomatic limb but really no overall benefit with the drug. Schwartzman, Robert Schwartzman, who is a neurologist who is now retired but really brought a lot of the experience that we have to the U.S., he was in Hahnemann or Drexel in Pennsylvania, but he really is one of the champions for ketamine in the U.S. And so he did a number of trials. The dosing that he used was obviously very, very low compared to what is being used now. But when he did an IV use in 19 patients, he noticed about 30% of patients received a reduction in their pain whereas only 2% of folks with a placebo reduced their pain. I don’t know how to say Sigtermans name correctly, I’m sure, but in a patient population of about 90 patients, or sorry 60 patients, ketamine versus placebo, they used a 100-hour infusion over five days, which is a fairly long clip to have something like that occur. But there was a reduction in the ketamine group of pain for up to 11 weeks after the infusion. And clearly they checked to see if there was any ketamine within the system and there wasn’t, but there was no significant functional change in these patients.

So when we look at other neuropathic pain disorders such as orofacial pain, this is obviously a case report. Eide and Stubhaug did an oral trial with an N of one, so obviously that’s interesting but not necessarily relevant. But they were able to show a reduction in pain intensity with swallowing, which can be important if you think about patients who have cancer and who have odynophagia. Baad and Hansen did a study of about 20 patients, IV use compared with placebo. They found no effect on spontaneous pain, which again, the data here is very, very mixed. And most of the studies are poorly done just so you know. And there’s a Cochrane review from 2012 as well that essentially says the same thing.

Rabben et al did an IM study of ketamine versus Demerol in about 30 patients, and there was about a third who received no relief from either, about a third who got prolonged anesthesia from both, and then nine out of 30 had transient relief with the ketamine as compared to the Demerol. When you look at their follow-up study when they switched this over to the oral formulation, and the idea simply is that the ketamine is, as I mentioned, available orally. And if you can successfully give somebody an IV trial and demonstrate success with that for pain relief, then potentially giving them the oral medicine afterward would be the continuation of that medicine so they can continue to have relief. And people have tried that with memantine, which is also an NMDA antagonist. They’ve tried it similarly with mexiletine historically, which is an anesthetic. But they would give IV formulations for neuropathic pain, and if the patient found benefit, they would switch them over to the oral. [Unintelligible 28:20] the oral really doesn’t have the same profound effect in patients but can be and those two did respond as seen here in this slide.

When used for phantom limb pain, Nikoljsen used the IV ketamine for limb pain, phantom limb pain, ketamine versus placebo in about 11 patients, and they noticed a reduction in residual limb and phantom limb pain in those patients with an overall increased pressure threshold. So they could tolerate more pressure. Why that might be important is in patients who are placing their residual limb in a prosthesis, that increased pressure threshold may allow them to tolerate the prosthesis better than they otherwise would, which can be helpful. Eichenberger did another study of about 20 patients, ketamine versus calcitonin versus ketamine and calcitonin versus placebo, and what they noticed is there was a reduction in phantom limb pain overall. And so that’s consistent with what we’ve seen anecdotally in our patient population as well.

So in terms of ischemic limb, and if anybody, I help with the inpatient pain service and so ischemic limb is one of the few disease states that when it comes in, it’s very difficult to manage even with IV PCA or PCEA, so opiate formulations with adjuvant medications despite those high doses, we have a very difficult time controlling those patients’ pain effectively. But with ketamine versus morphine, Persson et al found in a group of eight patients that the ketamine group gave complete relief in eight out of eight patients whereas the morphine gave complete relief in five out of eight patients.

So continuing on with this, Mitchell and Fallon used this in about 35 patients where opiates plus ketamine versus opiates versus placebo. And in the ketamine group, there was a 65% improvement in pain 24 hours post-infusion, and then about 70% had pain relief about five days after infusion with improved general activity and enjoyment of life, which is, I think obviously what all of us are trying to accomplish for our patients.

Looking at fibromyalgia, the dosing for fibro is generally much lower. Sorenson et al did an IV study in 18 patients where ketamine was compared with morphine versus just lidocaine versus saline. And there was improved pain intensity with the ketamine. It was decreased tenderness at tender points and increased endurance so they could tolerate more activity. As anybody knows, patients with fibromyalgia fatigue quickly, which prevents them from doing things like their activities of daily living.

Graven and Nielsen did an IV study of ketamine in 29 patients where they compared ketamine versus placebo. And about half of those folks responded and they were actually then double blinded for ketamine versus saline. In the non-responders, there was a reduction in pain at rest, referred pain, and muscular hyperalgesia which is one of the hallmarks for fibromyalgia.

And then Noppers et al did a study in about 10 patients with ketamine versus Versed, and that was considered the placebo arm. They obviously, placebos are difficult because we know that ketamine has an effect cognitively on the brain so using a comparative placebo is difficult, and Versed was felt to be enough of a cognitive disturbance that it might mimic ketamine’s effect, and so at 15 minutes with increased plasma concentration, the ketamine group, eight of those had greater than 50% relief versus three of the Versed group.

So again, these studies, if you think about it are extremely small and that’s the biggest limitation is most of these studies are going to be less than a hundred patients, and with that, it’s hard to make any real conclusion about the effectiveness of this therapy. But most of these tend to be positive and that’s obviously why we need more data.

This is something that we did locally here, and it was really more, our IRB and for anybody on an IRB, please don’t shut down any work we’re doing, but I think our IRB has an exclusion that you can get an exclusion for your current exemption, sorry, for you research if you have less than six patients. And [inaudible 32:56] we had six patients who had complex regional pain syndrome. We stopped. But we were looking essentially at how patients did and whether they would be able to be weaned off or reduced on their opiates by using ketamine.

And so we had the average patient was on about 151 mg of morphine equivalent before ketamine for their complex regional pain syndrome, and afterward they were on about 18 or about close to 20 mg of morphine equivalent. And that was still accompanied with a change in their visual analog scale from an average of about six and a half to about three, so about 50% reduction. So again, a very, very small study, but again the trend is in the positive direction and something that we thought would be useful. My understanding is the National VA is using ketamine as a means to detox patients altogether. I did see some of their slides and it’s pretty impressive. I don’t know who else is doing that but that is also a mechanism that ketamine is being used to just detox patients off of opiates altogether.

In terms of what we use here at GLA, at West Los Angeles, so we use this for complex regional pain syndrome as I mentioned. We have several patients with deafferentation pain due to motorcycle accidents where the limb was traumatically removed but with a stretch injury to the brachial plexus and lumbar plexus, and so these are also very difficult patients to manage. We’ve used it in ischemic limb and phantom limb. We haven’t used it in fibromyalgia yet, meaning patients who got ketamine, had fibromyalgia but their primary disorder was something else. And so we’ve had that as a co-occurrence. We didn’t really delve into that too much. We used it for central headache and it’s been effective for that.

We’ve also worked with our palliative care colleagues for cancer pain. One of the cases, and this is something that I didn’t even anticipate, palliative care asked us if we could be involved with a patient who was really doing poorly, wasn’t tolerating the medications well and was very sedated because of the opiates that they were receiving as well as the adjuvant. We put them into our protocol and started IV ketamine for them, and the problem was one of the things that does happen, you can dissociate a little and this gentleman felt like he was floating to heaven. And so he felt it was so uncomfortable, even though we did give him a significant amount of Versed, he felt it was so uncomfortable for him that we had to stop the infusion after about two hours. So that was something that I never even anticipated as a possibility or a limitation, but things like this do happen. And we’ve also used it for other neuropathic conditions including MS with good relief.

So exclusions that we use. Anybody who is pregnant or is lactating, it is found that the drug does cross the placenta and can affect the newborn or the fetus, so we have to be very careful with that. If we do use it in women, obviously we do a pregnancy test each and every time before we do the infusion. Anybody with uncontrolled hypertension, anyone with a history of psychosis or uncontrolled psychiatric illness because, again, this is a PCP analogue and it can cause patients to have significant mental health problems, folks with a history of heart transplants, elevated intraocular pressure that’s not controlled. So if they have glaucoma and they’re well controlled then there’s no contraindication. Anybody with an altered mental status, and I would argue that the gentleman we took for cancer pain that I mentioned earlier probably was altered and that’s one of the reasons he couldn’t quite participate, but I think that is certainly understandable and we were just reaching for straws at that point. Obviously, anybody with a hypersensitivity to ketamine, but that’s difficult to know until you try it. Folks with porphyria, ulcerative cystitis. Long-term use with this medication, especially in recreational users, has demonstrated this propensity towards causing cystitis-type symptoms. And so if you have this disorder already or you have significant problems with cystitis, then this may not be a good medication. And then there’s the, this endocrine society has sort of said that ketamine may not be a good medication for folks with thyroid disorder. That’s sort of a blanket statement. It’s not that we have really precluded anybody with thyroid disorders from getting this medication, but it is something that is in the literature and should be considered.

So we have two beds available to us. They’re not concrete beds. They're basically two beds that we can use in the CPC. We arranged for this beforehand. We have a nurse dedicated to the infusion, so the four hours of infusion is occurring, she’s at the bedside with the patient. Usually she’s doing other work as well as monitoring, but she is dedicated during that time. So it’s fairly labor intensive. The patient has to be NPO before the infusion. We have them on a telemetry so there’s continuous EKG, a blood pressure that’s every 15 minutes, and then pulse oximetry as well. We do keep them for one hour prior to discharge just to make sure they’re okay. We usually allow them to, we actually encourage them to eat at that point before they leave. And then they have to obviously bring a driver. They can’t be driving by themself. So in terms of how we follow our protocol, the patient is first evaluated in our pain clinic. There’s a discussion with the multi-disciplinary team, and that’s psychiatry, psychology, anesthesia, neurology, and PM&R amongst others. So that’s the group that discusses whether it’s something worthwhile to proceed. And so if everyone okays it or we think we still need to do a little bit more work before starting it, we do that.

Our ketamine protocol is essentially 40 mg per hour for four hours. That’s where we generally start. Some of our cancer patients have been fairly cachectic, and so we’ve started it at much lower doses based on a milligram per kilogram dosing, but generally speaking, 40 mg per hour for four hours. We pre-medicate with midazolam, 1 to 2 mg IV push. We do allow that every two hours as needed. Clonidine is started before the infusion because they will become, they may become hypertensive. Again, many of our patients are young and so they have a nice response to this as well, so they manage their blood pressure. If we need to use labetalol we can use that. That’s a PRN. And then for any nausea that occurs, we use Zofran 4 mg IV push.

The other thing just sort of basics of this. We have the patient bring dark sunglasses in. They’re in a CPC setting where there’s recovery for folks who’ve had colonoscopies, endoscopies, bronchoscopies, so there is lighting in that area and so we ask them put on very dark sunglasses so that they really can sort of zone out. If some of the patients are interested in listening to music, they’re encouraged to bring headphones. I try not to have them bring any sort of music that’s violent or too difficult to manage because any of that stuff can become part of their dreams if they do have dreams during the ketamine infusion, which most of them do. The gentleman I pointed out at the very, very beginning of my case report, he liked to listen to ZZ Top, so that was his thing. So every time he would show up he would come in with his headphones and his iPhone and listen to ZZ Top, and that put him in a good place and we definitely encouraged that.

The gentleman who is getting ketamine today, or yesterday and this week, he’s a young 33-year-old gentleman with complex regional pain syndrome of his left leg. He brings in, I think, classical music. But this is another gentleman who, again, saw us about two years ago, who had complex regional pain syndrome, couldn’t get the care he needed in Wisconsin at the facility he was at, so they asked us to get involved. And we’ve had him come basically once a year for three ketamine infusions, and then he goes back to Wisconsin and lives his life really in pretty good pain control, no opiates, and does quite well for around anywhere between seven to about nine months and then comes back in for another repeat infusion. He’s gone on to working on his MBA. He’s back to work. He’s fathered a child. He asked me yesterday if he should get a vasectomy, which I kind of [unintelligible 41:59] the idea was that if he has complex regional pain syndrome and he has a vasectomy could, hypothetically, this lead to complex regional pain syndrome of his pelvic area? And so I encouraged him to consider ketamine or possibly a sympathetic block before his vasectomy. When I told him that, he decided he just wasn’t going to have the vasectomy. So that’s kind of where he is. But we do see this pretty routinely in patients and they do fairly well.

So with that being said, points for further study. We know that ketamine is useful in some neuropathic pain syndromes. We need more studies with a better protocol. We need to have a better understanding of all the relevant mechanisms of action. We have a pretty good understanding of where the drug works, but I think we need to hone in on this a little more. And if we can decrease side effects, perhaps by using the S-stereoisomer to get that effect, maybe that would allow some of the reduction or using other adjuvants that might facilitate ketamine at even lower doses. So those are things that I think certainly need to be looked at.

The feasibility of repeated infusions. Now this is quite expensive. In the U.S., anywhere between $400 to $2000 is charged outside of the VA for infusion, so it is quite expensive if you are having repeat infusions. There is a lack of efficacy in topical, and perhaps there is a way of making that more, maybe making it better with different types of introductions into the system, whether it’s things like DMSO or other things that carry the ketamine into the system. It would be interesting to know more about that because then we could use it topically and we could use it locally in areas that are problematic for those patients who just have areas of tenderness or significant pain which we can’t control otherwise.

The role of oral ketamine and the possible risk for diversion and abuse, I think that’s always a concern, especially today with the environment that we’re in. And then addressing the concomitant depression that’s associated with pain with this drug I think is also important.

So with that being said, that’s all I have actually. That’s my last slide, so I think, hopefully I covered most of the pertinent topics, but that leaves us with 15 minutes for questioning or discussion that you guys may have.

Dr. Robin Masheb: Thank you, Dr. Pangarkar. This is a great presentation, and we do have a few questions that have come in. And I just want to encourage our audience to keep writing in and I’ll keep track of those questions. One question that we have here is about precautions about trying to prevent addiction or whether addiction is related to these ketamine infusions and if you could talk about that generally.

Dr. Sanjog Pangarker: Yeah, that’s, I mean that’s a great question and certainly something we’re also worried about. We’ve had patients who we felt didn’t get significant relief, meaning their pain scores didn’t change much, their function didn’t change much, but they continued to ask for more infusions. And so do patients inadvertently get addicted to ketamine? I think it’s certainly possible. I think the literature does support that ketamine is an abusable drug and many folks have become addicted to it with street use.

And so whatever sensation it is, the psychomimetic effects that this drug has some people generally like. And so I think in this controlled setting, we try to look for those things. And that’s part of the reason we have that multi-disciplinary approach to looking at each of these patients and making sure that we’re not going down the wrong road with this patient and offering them this treatment out of our desperation that we’re not getting the patient better. But meanwhile we’re making the patient worse. So that’s definitely a consideration and one of the reasons we do have a multi-disciplinary clinic looking at these patients closely. But good question and definitely a concern of ours.

Dr. Robin Masheb: I noticed that in terms of the different types of pain that you listed that you didn’t have anything specifically about back pain or arthritis pain. And can you talk about what would be the reasoning for not using ketamine for these types of problems?

Dr. Sanjog Pangarker: Sure. And I think you can use it. So that’s a good question. I’m trying to figure out how to answer that question correctly. Our emergency room does use ketamine for patients who come in with acute pain. And that could be from a fracture or something to that effect, so I don’t want to give the impression that ketamine doesn’t benefit folks with nociceptive pain. But really if the transmission process of pain signaling from the periphery to the central nervous comes through the nervous system, what we’re really trying to do is modulate that nervous system so that it doesn’t become broken or the pain signal doesn’t stick.

And so I think that this treatment can be helpful certainly in neuropathic pain states. It can be useful in nociceptive pain, too, but I think, and there are studies that looked into this is how to prevent acute pain from becoming chronic pain. But I think most of us would shy away from using ketamine routinely for just something that comes in. It’s really the patient who has few options for treatment who comes in with nociceptive pain, fracture pain, that kind of thing. And back pain, as you know, is a symptom more than a diagnosis, and so there’s a lot of movable parts in the back and parts that may be causing the pain symptoms. There’s also the psychological or biopsychosocial aspects of back pain that really also have to be addressed simultaneously, so most of these patients that we’re using or considering for ketamine have really been at the end of their rope and have used this treatment for those reasons.

And I think that’s a little bit unfair for ketamine in itself. If you think about, if you have the most recalcitrant cases coming in and the only time you use ketamine is for these really difficult scenarios, then obviously the success rates will probably be low because they failed a lot of other things already. But the question is how open should we make this treatment algorithm for less dramatic pain, I don’t know. And then some of that goes to the addiction issues. Some of that goes to the monitoring issues. And it’s just really difficult to get ketamine approved, and it took us almost two years to get it approved at our facility. And once we were able to demonstrate that we didn’t cause people to freak out and throw furniture, I think people were okay with us using it and they sort of left us alone. And we’ve been pretty successful. I mean I think about 70 or 80% of the cases we’ve done, we felt that we made a meaningful impact on that person’s life. But we haven’t tried it really in nociceptive disorders.

Dr. Robin Masheb: That’s great. I have quite a few technical questions about dosing and administration, so if I can, I’ll kind of put all of those together to you. One of them is do you have experience giving ketamine intranasally? Another is do you still have to monitor patients with EKG if you’re doing the subcutaneous injection infusion? Another one is, I know you had given some information about dosing, but another one is about the dose and duration, kind of what is considered optimal and do you, in your experience, notice that higher doses and/or longer infusions correlate with longer pain-free periods of time?

Dr. Sanjog Pangarker: So those are all excellent questions. I have never used intranasal ketamine for anybody. That’s not to say there’s not literature. There is literature to support intranasal use of ketamine, and so I don’t know that literature very well, so we haven’t really investigated it. As I mentioned, the oral forms of ketamine which are prescribed in certain clinics and university settings as well, not really so much in our VA. We don’t do that but I know some VAs do. But I don’t know much about intranasal ketamine or how effective it is, but there is a significant first pass with oral stuff and that’s what I think limits its success rate plus most of us are worried about putting an abusable drug out on the street or potentially putting it on the street. So I think I can’t answer the question well about intranasal, but I know that it is used orally for some patients.

In terms of subcu and monitoring, most of where I’ve seen subcutaneous use of ketamine is really in the palliative care setting. And because of the context of palliative care, those patients haven’t been monitored with EKG, but that’s the only way I’ve actually seen it happen in our scenario. But I can’t really answer that either. I think that if you were using it for pain relief in an otherwise functional person, I would really want them to be monitored on EKG whether they’re getting it subcu, IV, or IM, at least for a period of time. But that would be my hope at least for our facility.

In terms of using the dose and duration, do increased doses and longer duration of treatments offer better relief? That’s a tough question but it’s a really fair question. So when this treatment was first, I think, thought about in Germany, for instance, they were using ketamine comas, right? So they were putting patients into an ICU setting, putting them on a ventilator, and then putting them into a ketamine-induced coma for about five days for complex regional pain syndrome. And they had amazing results, meaning they had close to 100% success rate with pain relief, and those patients came out of it feeling pretty well and it also was sustained for a period of time meaning, I want to say a few months.

What we’re seeing is by using what we do here is completely different is we do three times a week and then we just stop. Meaning we do Monday, Wednesday, and Friday, and that’s really a function of our manpower limitations. And then we just see how that patient does. So if they are doing well, then we can continue it for a period of time. If they’re not doing well or haven’t found any benefit, we usually will discontinue it. But what we’ve seen in the right patient when selected at the right doses, and that’s another part we’ll go into, but these folks get an additive effect and they get longer relief. We tend not to go greater than 80 mg per hour. But there are definitely clinics, and the person I work with, Joshua Prager over at UCLA, he uses much higher doses than I do. But he is an anesthesiologist by training; I’m a physiatrist. And so he feels more comfortable going to higher doses. I think 80 mg is where I feel comfortable. That’s my, essentially my maximum dose. And then we follow those people essentially for four hours. We’ve got about three months of relief with our three day, with our three times a week use for these patients, so that’s the average benefit that we’ve seen, about three months.

Like this gentleman who came from Wisconsin who is with us, he gets anywhere between seven to nine months if not a little bit longer of good relief. And again, the key component is that while you’re doing ketamine and as this patient is transitioning back to their regular life, they need to make sure they have psychological counseling for whatever the pain disorder is and also physical therapy to sort of, as a multi-disciplinary pain program to keep them going so that they can use resources other than just a passive treatment like ketamine to prolong the effect. But there are folks who advocate bigger doses for longer periods of time. I don’t think that the literature fully supports that though. If anything, the doses that Schwartzman was using were so small, even compared to what we use, with good relief for many patients that I don’t think you necessarily have, you need to go bigger is better.

Dr. Robin Masheb: I have a lot of questions about the case that you presented in terms of the dosing which you mentioned, the 80 mg, how long you do it, how frequently, how much did the patient weigh. Are there any other details you can share with us about that case and the treatment?

Dr. Sanjog Pangarker: Sure, yeah. So ketamine, it is dosed as a milligrams per kilogram and that’s what probably most anesthesiologists are comfortable with and have used. So depending on, and I didn’t want to get too heavily into that because that’s really sort of more book data you can look up that generally speaking you can use .5 mg per kg. Administrated this over 30 minutes in an acute setting, and you might find some benefits with these patients. But I don’t really, I haven’t found that that makes a significant difference. If I truly am just seeing as a dose finding effect, we start at 40 mg for essentially everybody. And that’s what we did with Mr. D, the gentleman in my case report. We started at 40 mg. Our final dose was the 80 mg dose. And so we did that probably the last five times that we had him.

The other issue is, of course, when somebody has effects like the gentleman who is getting ketamine now who has complex regional pain syndrome, he’s 32 or 33, he had side effects at 80 mg so we backed him down to 60 mg per hour. And so it’s really trying to find out, he’s 268 pounds, the gentleman who we’re doing right now. So if you look at it, his 60 mg is a very small dose, or a relatively small dose. I shouldn’t say it’s a small dose, but it’s a relatively small dose for his size, but it is effective for him. So for pain relief, at least for chronic neuropathic pain, I don’t think it’s the same one to one as we see in the anesthesia literature where it’s sub-anesthetic dosing .15 to .3 or even .5 up to a maximum of one. But that’s how I’d answer that. I think you can look that kind of stuff up in a book, but to be effective, you just have to figure out what the dose is for that particular patient. Go low and go slow with your dosing just to be safe.

Dr. Robin Masheb: Great, so we just have about two more minutes. I think I’ll give you one more question and then we’ll need to wrap up because this should be a short one. Does ketamine have any anti-inflammatory effects or properties?

Dr. Sanjog Pangarker: So that’s a really good question. We talked about this. Really a significant number of mechanisms that this drug works with and I think there are anti-inflammatory properties but not in the conventional sort of arachidonic acid way that we think about in terms of like NSAIDs and things of that nature. Because what we do see is when these limbs, if you will, for complex regional pain syndrome when they come in, they’re fairly swollen. The ones that we typically see that are not atrophic will be relatively big. They’ll be red and meaty and certainly different than the other side. And we’ll see over the course of our infusions that the redness and the swelling begin to subside and begin to reduce. And so I think there is an anti-inflammatory effect. How exactly the anti-inflammatory works, I don’t know. It is considered a neurosteroid. As you can see at the very bottom of this slide, it is considered a neurosteroid. And does it have an anti-inflammatory effect that capacity, I’m not sure. But I do believe it does have an anti-inflammatory effect in some, with some mechanism that I don’t fully understand.

Dr. Robin Masheb: Thank you. And thank you, Dr. Pangarkar, for sharing your work with us today. This was a really exciting presentation. We had some great questions from the audience. Just one more reminder for everyone to hold on for another minute or two for the feedback form. If you’re interested in downloading the PowerPoint slides from today, please go to the reminder email you received this morning. You will find the link to the presentation. If you’re interested in downloading slides from any of our previous sessions, simply do an internet search on VA Cyberseminars archive and use the filters to find our previous seminars. You will be receiving an email with your certificate of attendance for today’s session. And please keep in mind that our next Cyberseminar will be on Tuesday, February 6th, by Drs. Tom Emmendorfer and Friedhelm Sandbrink. The title of that presentation is VA Opioids Safety Initiative: How did we get here and what is ahead? You’ll be receiving registration information around the 15th of the month. And I want to thank everyone for joining us at this HSR&D Cyberseminar, and we hope you’ll join us again.

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